· O H I O · W E S L E Y A N ·

Technical Report

Functional Assessment of Laser Irradiation

David O. Robbins, Ph.D.

March 1988

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Vision Laboratory
Department of Psychology
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FUNCTIONAL ASSESSMENT OF LASER RADIATION

ANNUAL AND FINAL REPORT

DAVID O. ROBBINS, Ph.D.

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Exposure of the fovea to intense coherent light can produce either transient or permanent changes in the eye's ability to resolve fine spatial detail. Permanent functional changes can occur in the absence of gross morphological damage and at power densities below the ED_{50} level. Furthermore, the eye may become increasingly susceptible to damage after repeated low-level exposures which initially produce only transient effects. Independent of any long-term hazards, laser exposures can also disrupt visual/motor behavior for periods of up to 96 hrs.

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FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals", prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication no. NIH 78-23 Revised 1978.)

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INTRODUCTION

The development and use of lasers has grown significantly over the past several decades and its continued proliferation is almost certain. The laser has become an economical alternative to other more conventional technologies in a wide range of diverse industries and in some areas, like telecommunication, photography, medicine, and chemistry, it has been the vehicle for technological advances which would have otherwise been impossible.

Newer laser systems, capable of delivering short pulses of both visible and invisible radiation, are significantly more powerful than their original counterparts. As a consequence, they pose more serious health hazards and create the need for greater protection for those who might be accidentally exposed.

Any bodily organ which can absorb the incident wavelength has the potential of being damaged. A tissue's damage threshold will be dependent upon the amount of energy absorbed, its dissipation over time and the physical characteristics of the tissue itself. Overabsorption can result from a brief, single exposure or from multiple exposures to energy levels which initially might produce no observable consequences. The eye, a delicate organ and photodetector by nature, is especially vulnerable to morphological alterations. Dependent upon output energy and wavelength, damage can be restricted primarily to the cornea or to the electrochemically active retina. While damage to the cornea can be extremely painful and can alter the transmission properties of the cornea, damage at the retinal level can produce either temporary or permanent blindness.

For the soldier, even temporary visual impairment could jeopardize the individual's ability to complete a visual-motor response and thereby imperil himself or his fellow soldiers from the successful completion of a mission. Hence, the establishment of safe operating guidelines, development of protective devices against accidental exposure, and the determination of the visual consequences of retinal exposure must remain a high priority in any laser research program.

As a first step, the minimal energies necessary to elicit ocular damage must be derived using a variety of acute and chronic exposure conditions. These thresholds can be determined by traditional morphological means (fundoscopic or histologic verification of tissue damage) or can be defined in terms of changes in the visual sensitivity (behavioral or electrophysiological analyses of retinal function). In many ways the latter criteria may be the most important since they relate more directly to the ability of an operator to successfully complete a visually-guided response. Furthermore, legal liability for treatment and provisions for disability will ultimately depend upon the demonstrated presence of perceptual dysfunctions.

Historically, the first attempts to delineate the effect that intense light has on the eye dealt with solar retinitis, retinal damage incurred while watching a solar eclipse (1). More recent studies have included examination of more focused, intense incoherent light sources such as the xenon arc lamp. With the invention and ultimate employment of lasers, attention has shifted to this type of light form since its potential for damage as well as possible therapeutic value greatly exceeds that of all other light forms combined.

Technological advances in other fields such as histology and electrophysiology have also greatly improved the analytical methodology for assessing fine retinal damage. Associated with these methodological changes has been the demonstration that moderate as well as intense light can produce permanent changes in retinal morphology (2, 3, 4). But predicted and observed damage thresholds have become inconsistent, in part due to differential sensitivities of various assessment techniques. Additional inconsistencies have resulted from the growing diversities within delivery systems and wavelengths of new laser devices. For example, histopathological examination (5,6,7,8) reveals retinal damage at lower exposure levels than are observed by ophthalmological examination alone especially when the area of retinal involvement is restricted. Furthermore, the photoreceptor outer segment has become the primary damage site (9,10) when low energy levels are employed. The isolation of initial damage at the receptor level is significant since this is also the site of the initial transduction of radiant energy to electrochemical energy, a process that is fundamental to the whole basis for vision.

Safety thresholds based on functional criteria are often considered to be the most sensitive, especially when considering wide field stimulation since subtle enzyme, photochemical and minute structural changes can cause shifts in visual sensitivity in cases where observable morphological disruptions are difficult or impossible to detect.

Even with functional criteria, however, thresholds for permanent shifts in visual sensitivity have varied depending upon the visual task used to assess function. Changes in the luminance, wavelength and contrast of test targets have yielded various damage thresholds but most are considerably lower than those derived using traditional morphological criteria. Relatively recent improvements in behavioral techniques for assessing functional impairment (11) have even further lowered the damage threshold and provided the opportunity for the examination of the transitional zone between temporary and permanent shifts in visual acuity. The elimination of anesthesia

for placement of laser exposures, which was a part of all previous behavioral studies, has allowed for the measurement of transient acuity changes during the initial phases of the recovery process and the exploration of power levels below those that produce permanent shifts in visual functioning. The present report utilizes this methodology for exposing awake, task-oriented animals. Prior to this effort, virtually no exploration of lower energy densities had been conducted. Instead, early behavioral studies were restricted to the evaluation of severe morphological disruptions resulting from light stimulation significantly above the ED_{50} (10, 12, 13, 14). The effects of these irradiation levels were usually permanent, producing impairment in visual acuity ranging from 40% to 80% of pre-exposure levels.

The nature of any physical damage is dependent not only on the characteristics of the laser but also on those of the target tissue. Historically, three somewhat different damage mechanisms have been demonstrated in light sensitive, biological tissue: 1) thermal 2) mechanical and 3) photochemical. In the case of the eye for instance, since it is a spectrally selective photodetector, the quantal efficiency of the particular wavelength employed becomes a factor influencing the site and severity of the damage. Other factors known to affect damage include the thermal properties of the eye (e.g. diffusivity), retinal position, and the energy density, duration, and spatial extent of the exposing beam. Because there are so many factors involved, no clear boundaries for each type of damage mechanism exists and, in fact, there are thought to be several transition zones where more than one mechanism is operating. For instance, it has been suggested that thermally enhanced photochemical effects may occur when tissue temperature rises themselves are inadequate to cause thermal injury.

Thermal damage occurs when the radiant energy of incoming photons is absorbed by biomolecules (mainly melanosomes of the retinal pigment epithelium or RPE) and is converted to heat, resulting in a temperature rise of at least 10^{o} C over ambient temperature in the neural retina, RPE and/or choroid. Such temperature increases prompt the denaturation of proteins with loss of tertiary structure and possible polymerization. Temperature increases of greater than 10^{o} C may cause irreversible denaturation, with permanent loss of tissue function. The thermal mechanism is a rate process (15, 16), a fact shown both empirically (17) and in the many theoretical models of the mechanism that exist (18). Birngruber (19) demonstrated that temperature rise is a function of various parameters of the exposure including its energy density, duration, and wavelength, as well as a function of the optical and thermal properties of the biological tissue. Because of the time-energy interdependence no one threshold can be established, but generally thermal injury cannot occur for exposure durations of less than a microsecond. Models also predict a direct relationship between spot size and temperature rise and equilibrium time which has been confirmed empirically by Cain and Welch (20). Generally, the larger the retinal image of the beam, the lower the power density needed to form a threshold lesion. Thermal lesions are generally homogeneous due to significant thermal diffusion, although they may be smaller than the laser beam size since maximum temperature and therefore maximum damage occurs in the center of the laser beam image.

Mechanical damage occurs in the retina when high power, short duration exposures cause the propagation of sonic waves in the ocular tissue. The pressure front generated within the RPE and/or choroid may cause microexplosions in, for example, receptor cells. Damage may then occur as the result of displaced bulk. Vaporization may accompany the mechanical effects, resulting in the formation and collapse of large cavities, which are often seen as splits in the inner plexiform and nerve layers. Mechanical thresholds are inversely related to time, with thresholds lowest in the picosecond range. Lesions caused by mechanical insult are less homogeneous than thermal lesions, tending to follow the spatial distribution of the energy in the exposure.

Generally, photochemical damage occurs at thresholds too low to cause thermal or mechanical injury (3). The exposures tend to be relatively long, at shorter wavelengths (21), and at low power densities. Again, there is an inverse relationship between duration and irradiance for photochemical damage. The reactions causing photochemical damage are not well defined. Basically, alterations in the biochemistry of the retina prevent the natural cyclic mechanisms of the photoreceptors to continue functioning normally. Several chromophores may be involved. Whereas the results of thermal and mechanical injury are immediately observable, photochemical insult may develop more slowly (22, 23). There have been no direct systematic studies to examine any differential effect these damage mechanisms may have on visual sensitivity.

Due to the nature of laser safety investigations, the use of human subjects poses serious methodological and ethical problems that are not easily resolved. As a consequence, intentional human laser exposure has been limited to those eyes that suffer severe retinopathies or eyes which are slated for enucleation. The degradation of such eyes as well as the usual medical urgency for their removal prevents the performance of complete postexposure testing on these subjects (24, 25). Therefore, for behavioral studies, a suitable animal model had to be found.

The selection of the rhesus monkey was based on the similarity of its retinal anatomy and physiology to that of the human and its comparable visual sensitivity. Some discrepancies do exist; for example, the rhesus retina may contain slightly different photoreceptor densities than man (26). Also, the spectral transmission of the rhesus eye favors the shorter wavelengths as compared to the human due to differences in the lens and macular. The rhesus eye may be a more efficient collector of light energy given its greater pigmentation, more transparent lens (27), and relatively larger pupil (28). Accompanying these structural differences are some functional differences. For instance, at low luminance levels the rhesus perform as if they are receiving 4-5 times more light than human observers. The maximum acuity that can be reached with scotopic vision, however, is apparently identical in the two species, which suggests that the minimum dimensions of the scotopic receptive fields are the same. However, the maximum photopic acuity is not the same. After correcting for the difference in focal lengths, the acuity of human observers is about 17% higher than that of rhesus under maximum photopic conditions. A possible explanation may be the increased light scatter or spherical aberration due to a relatively larger pupil in the rhesus. Both species have distinct photopic and scotopic acuity functions that cross at the same luminance levels (28). The acuity differences that do exist are small and may be accounted for by optical rather than any inherent physiological differences.

Human and rhesus chromatic sensitivity have also been shown to have a high degree of similarity (29, 30, 31). Some investigators have shown however, that the long wavelength sensitivity of the rhesus is slightly less than that in normal human observers (23, 32, 33). This long wavelength insensitivity is especially pronounced when very fine acuity targets are used. Under these conditions the average rhesus sensitivity is more similar to that of a protanomalous human observer than a normal human trichromat (23). In spite of these small discrepancies, both the visual performance and retinal anatomy of the two species are remarkably similar, making the rhesus an excellent human prototype. Furthermore, the position of this animal on the phylogenetic scale and its implied superior intellectual abilities lead one to assume that the strategies employed by these animals to compensate for any lost visual function may not be significantly different from those employed by their human counterparts.

Using the rhesus as our animal model, the current effort has attempted to delineate the immediate and long term adverse effects that single and repeated exposure to Argon (514 nm), HeNe (633 nm), and Krypton (647 nm) lasers have on visual sensitivity. Various parameters of the exposure have been manipulated including energy density, duration, spot size, and position on the retina. Likewise, in an attempt to assess vision under a variety of photopic and scotopic viewing conditions, we have varied the background luminance, wavelength, and contrast of visual targets. Although much work has been done in this area, there is still much to be accomplished not only to protect human observers from accidental exposure but also to prevent underutilization of lasers because of unrealistic restrictions placed upon its employment. Of particular concern are the consequences of repeated exposures at levels below the ED_{50} for the single exposure condition. In addition, as new laser systems are produced, new standards should be developed to account for any changes in output energies, wavelengths, and/or durations.

METHODS

A detailed description of the methods used to expose awake, task-oriented rhesus monkeys has been presented elsewhere (34) and will be only briefly described here. This method has reliably produced foveal exposures in conscious animals.

Subjects. Male rhesus monkeys ages 2 through 8 years and weighing 8 to 10 lbs were used as experimental subjects. All animals were examined fundoscopically prior to exposure and, together with preexposure measurements of visual acuity, revealed no refractory errors or morphological abnormalities in their retinae.

All subjects were housed individually in standard primate cages and were free to move about in their home environment. Animals were fitted with a lightweight, plastic neck collar for capturing purposes. The home environment was enriched with a variety of activities including TV, radio and play activities during the daylight hours. Light/dark cycles as well as temperature and humidity were controlled. The animals' diets and liquid intake were monitored and animals were under veterinarian supervision. Each animal was routinely TB tested.

Apparatus. During the course of this effort a practical and inexpensive alternative to the standard primate chair was designed (35). This apparatus permitted easy removal and transport of animals from their home cage to the experimental chamber without the use of any form of anesthesia. Restraint was necessary to maintain the animal's correct line of fixation and distance from the viewing screen which was essential for both accurate measurements of visual acuity and proper placement of exposures on the central fovea. One of the major drawbacks to the

use of nonhuman primates is that they can be very difficult and even dangerous to handle. This is especially true as the animal ages and after laser exposure. Historically, when the experimental paradigm requires temporary restraint of the animal on a daily basis, chronic restraint devices such as primate chairs have been employed. Since the experimental test period extended over a period of months or even years, such a procedure was judged to be detrimental to both the welfare of the animal and the purpose of the experiment. Daily administration of anesthesia was also judged to be undesirable since it might not only disrupt experimental procedures, but also would be contraindicated medically.

In our procedure, the animals were conditioned to enter a specially designed squeeze device which easily converted to a temporary restraint-type chair. Prior to training, the animals were custom fitted with a lightweight Plexiglas collar. The animals easily adapted to wearing these collars and we observed no health problems or chafing in animals chronically wearing these collars.

The restraint device is shown in Figure 1. The front of the device consisted of a vertically sliding door which, when positioned against a similar sized door in the front of the animal's home cage, permitted the animal access to the device. The entire restraint device was mounted on an hydraulic lift platform attached to a mobile cart. Initially, animals were conditioned to enter the device to receive a food reinforcer. Once inside the device, the door was closed to prevent escape, the animal's head elevated, and the device moved into the test chamber. Once inside the test chamber, the animal was fitted with a Plexiglas helmet to minimize head movements. An opaque facemask with adjustable iris diaphragms was aligned with the animal's pupils so eye position could be tightly controlled. Small, voluntary head or eye movements could block the animal's line of sight with the viewing screen and result in the animal being negatively reinforced for incorrect detections. As a consequence, subjects learned rather quickly to remain fixed in position once aligned with the screen. Animals were also positively reinforced with either fruit or juice for cooperative behavior.

Laser exposures and visual assessments were made in the same light-tight, sound attenuated chamber. Both the experimental chamber and surrounding room housing the image and laser optical systems were painted black to prevent light scatter. A white noise generator was used to mask sounds generated by the experimental equipment. The chamber measured 70" x 26" and contained mounting brackets to lock the portable restraint device in position once proper alignment with the viewing screen was assured. Mounted on the far wall was a rear projection screen subtending 3 deg at a distance of 1 m from the animal's pupil. Two carousel projectors, positioned outside the experimental chamber, served as the source for image projection and the background of the viewing screen. Luminances and wavelengths of test targets and backgrounds were produced independently by neutral density and interference filters placed in the light paths. Both projectors were programmable and were internally able to read a variety of coded slides.

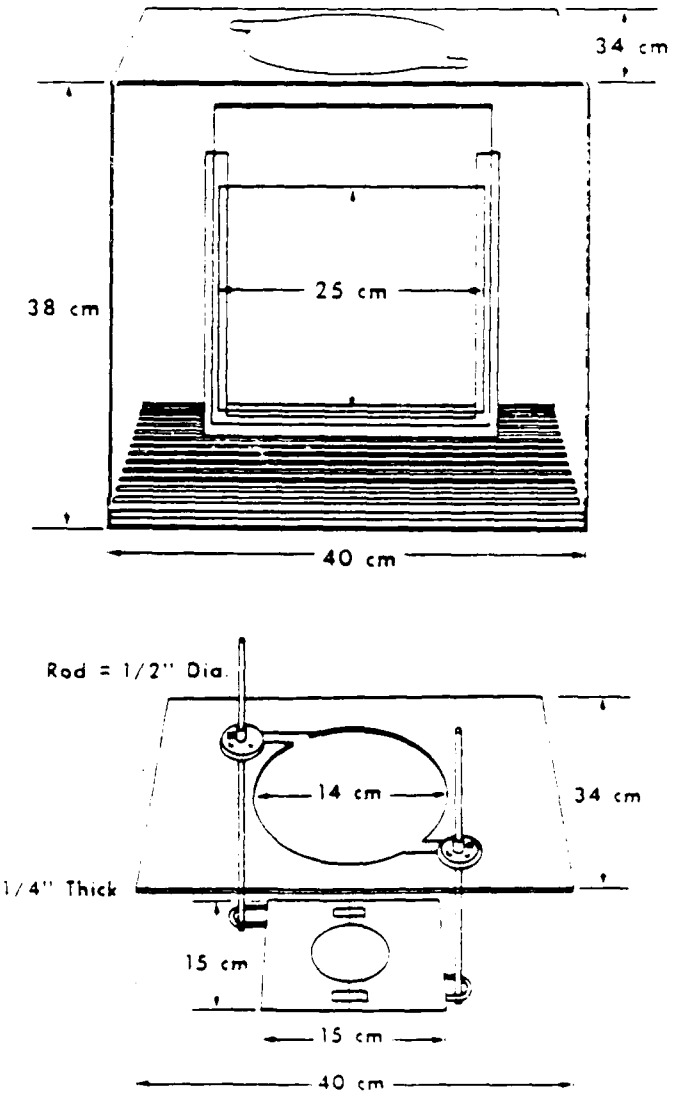

Figure 1. Diagram of the Plexiglas restraint device used during laser exposure and acuity testing. The overall dimensions of the cage, 40 w x 38 h x 34 d cm, readily accommodate rhesus monkeys of various sizes. A diagram of the collar, worn by the rhesus monkey, is shown in the lower diagram. Poles were used to draw the animal's head through the hole in the top of the device and secure the animal in position.

Acuity was measured using standard Landolt rings and square-wave gratings. Slides of the rings and gratings were photographically produced on Kodak high contrast film (Kodalith) and were photographically reduced to produce different size targets. The Landolt rings were black on a clear background. The thickness of the Landolt rings and the width of the gap that formed the critical detail were always 1/5 of the diameter of the ring. The size of the gap could be varied from 0.25 to 30 min of visual angle in equal steps. The position and orientation of the gap in the Landolt rings were always in the same location on the screen. Except for the screen, the test chamber was entirely dark. Similarly, square-wave gratings were of equal dimensions and their spatial frequency as well as orientation on the screen could be varied.

The presentation of slides, recording of the animal's responses, and consequences for the behavior were under the control of a BRS/LVE Interact System and Data General Nova 3 microprocessor. An Apple IIe microprocessor was interfaced with the Interact System for on-line data analysis, display, and storage.

Discrimination Task. Animals were trained using an avoidance paradigm to press a lever in the presence of a Landolt "C" or horizontal grating and not to respond in the presence of a gapless Landolt ring or vertical grating. Failure of the animal to press the lever in the presence of a Landolt "C" (defined as a "miss") or lever pressing in the presence of gapless rings (defined as a "false positive") resulted in the presentation of a discriminable tone and, on a variable reinforcement schedule, a brief, weak electrical shock. The shock was obtained from the secondary of a high-tension coil by discharging a capacitor into the primary, and was annoying but not highly painful as the author can testify from experience. Swinnen, Brady & Powell (36) concluded that because of its short duration this type of shock is safer than conventional electric shock. Our animals demonstrated no reluctance to enter either the restraint cage or experimental chamber also indicating that the shock had no lasting psychological importance. The use of negative reinforcement during testing was necessary in order to consistently maintain the animal's vigilance during the course of testing and especially immediately following laser exposure. A well trained and vigilant animal could avoid shock altogether.

Threshold acuity was derived using a modification of the von Bekesy tracking technique (37). In this technique, if the subject correctly detected the Landolt ring by pressing a lever (hit), a discriminable tone was presented and the next series of Landolt rings and gapless rings was 20% smaller. Incorrect detection of the Landolt ring (miss) resulted in a different discriminable tone, the possibility of a brief shock on either a fixed or variable ratio schedule, and the presentation of rings 20% larger. To discourage the animal from responding indiscriminately to all rings, a third discriminable tone was presented immediately following lever responses to gapless rings (false positive) and, on a fixed ratio schedule, the animal received a brief shock for these incorrect responses. The number of false positive responses was always low in trained animals (less than 10%). Using this paradigm, the size of the threshold target was always at the animal's threshold thereby eliminating time spent testing targets either significantly above or below threshold. The test objects were typically presented in sets of four rings that were of equal diameter. Three of the rings in each set were gapless, while the fourth was a Landolt "C" that appeared in a random position within the set. Each ring was projected for 2 sec. and there was a 1 sec. dark interval between successive rings. The size of the test series was shifted only on responses to Landolt "C" rings and not to gapless rings. Baseline means, variability, and false positive responses in both the exposed and control eye were monitored daily throughout the experiment. All measurements were made under monocular conditions and after the animal had adapted to the luminance level of the screen.

Laser System. Either a 4.0 W Argon laser (Spectra Physics, Model 165/265) or 2.0 W Argon laser with a Krypton plasma tube served as the primary exposure source. A small HeNe laser was used for aligning purposes. A diagram of the optical system is shown in Figure 2. The entire laser system, with the exception of a beam splitter and focusing lens, was mounted outside the experimental chamber. The "raw" laser beam passed first through several neutral density filters for attenuation and then through a manual safety shutter. The attenuated beam was then directed through an electronic shutter which produced calibrated flashes of between 1 and 100 msec when triggered electronically by the experimenter. The beam was then diverted by a 4.5 cm diameter front surface mirror and entered a beam expanding telescope which produced a collimated beam of adjustable diameter between 50 and 500 microns. The expanded beam was then directed through a final focusing lens and a 5 x 10 cm coated pellicle beam splitter was placed at the intersection of the diverging laser beam and the beam from the rear projection, viewing screen. The converging beam then passed through a final 4 mm aperture positioned just in front of the animal's natural pupil.

Mounted on the opposite side of the beam splitter was a diffuser and ultrafast photodiode (HPA 4203). The output of this detector was displayed on a memory oscilloscope and was regularly calibrated against an EFF Model 580 Radiometer placed at the

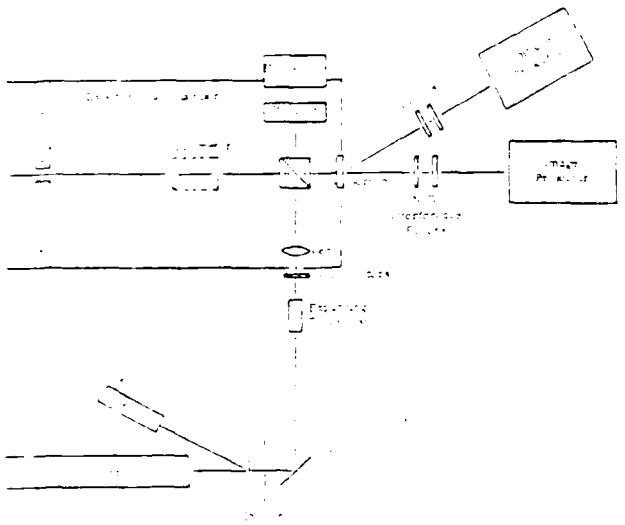

Figure 2. Diagram of the laser and image optical system. The laser beam was presented using a Maxwellian view and was coaxial to the gap in a threshold Landolt ring.

corneal plane. The power and pulse width of each laser exposure was measured and recorded.

Proper alignment of the laser beam with the animal's pupil was critical. The laser beam was presented to the animal coaxial with a line between the artificial pupil and the gap in a specified, threshold Landolt ring which subtended less than 1 minute of arc. For determinations of the line of sight, a 2 mm aperture was placed on the screen over the position of the gap in the specified Landolt ring. A mirror, approximately 2 m behind the 4 mm artificial pupil was then adjusted until it was normal to the line of sight. With the converging lens removed, the beam splitter at the junction of the image and laser beams was then aligned so that the collimated beam from the laser past through the 4 mm aperture and was reflected off the mirror back onto itself and through the 2 mm aperture at the projection screen. Coaxial alignments with the line-of-sight were then verified by noting that the reflected beam passed through both apertures and back on itself without any loss. The focusing lens was then positioned such that the cornea was in the focal plane of the lens and so as not to change the alignment of the beam with the line-of-adjustment. Presenting the beam in Maxwellian view reduced the possibility that changes in pupil diameter or small lateral movements of the animal's head would affect the amount of light entering the eye.

Corneal power densities of greater than 2 W over a retinal area of from less than 50 microns to greater than 500 microns in diameter was possible. The location of the exposure on the retina (on- or off-axis) could be varied by adjusting the position of the beam relative to the animal's point of fixation on the viewing screen.

Laser exposure. Prior to any laser exposure, stable acuity levels were established for each eye. Mean data, derived from a minimum of 14 different test sessions, was used to establish the acuity level for each of a number of different chromatic, luminance, and contrast viewing conditions.

Prior to each exposure, pre-exposure acuity was derived for each eye during a 15 - 20 min test session. Failure of the animal to obtain a mean acuity within one standard deviation of his predetermined acuity level aborted the laser exposure. Session variability or an increased false positive response rate beyond a pre-established level also aborted the session. In cases where the animal did not achieve his pre-exposure baseline level in an eye which had previously been exposed, testing was continued to establish the parameters of the visual deficit.

The laser flash was triggered immediately after the animal correctly detected a specified threshold Landolt C. (In previous studies using a closed circuit television, it had been observed that our animals maintain fixation on the critical feature of the target for several seconds following their motor response and until reinforced either with the discriminable tone or shock.) No exposures were made following incorrect detections of threshold targets or following correct detections during the final 1 sec of the trial. Using this procedure immediate and significant downward shifts in acuity were noted in over 90% of the exposures presented. In those cases where no such downward shifts in acuity were noted, it is possible that involuntary or pre-established voluntary eye movements may have led to exposures in the peripheral regions of the retina. Given the nature of our acuity task, exposure of this region of the retina would have been difficult or impossible to detect. Control or sham exposures with the laser beam blocked at the point of the safety shutter tested for any factors within the procedure which might change the animal's expectancy and response criterion.

Typically, only one exposure was made per session and in cases where the animal failed to return to his pre-exposure level during the immediate postexposure session, no exposures were made in subsequent sessions until a new baseline acuity level was established. At each power density, a repeated, random design was employed for each of the different types of viewing conditions employed. The order of laser power densities presented was fixed, beginning first with the lowest and increasing in a stepwise order following completion of all viewing conditions. Postexposure testing was terminated after the animal had regained his pre-exposure acuity level for the given viewing condition or after 2 hrs of testing whichever came first. The animal's unexposed eye

analyses of shifts in acuity were made for each exposure under each viewing condition. Since the number of exposed animals was relatively small, between subject analyses were limited and the majority of the analyses were made within subjects. Statistical comparisons were made of the changes in the degree and duration of the initial deficit as well as the total time for full recovery as a function of different exposure energies, durations, spot sizes, and wavelengths. Also examined was the effect the specific acuity task had on the magnitude and duration of the visual deficits.

The determination of the animal's performance level using the tracking technique was derived using the formula developed for the "Up and Down" procedure (38). Normally an animal's acuity was averaged for each running two minutes of testing before and after exposure. This data could be graphed in terms of the "Up and Down" procedure (raw data), in terms of average visual acuity, or more commonly, percent deficit from it pre-exposure baseline mean.

RESULTS

Sample raw data using the tracking technique is shown in Figure 3. In the upper portion of this figure, four different luminance levels were used to demonstrate the influence of luminance on acuity as derived by the tracking technique. Horizontal excursions represent the presentation of Landolt "C" trials and the animal's responses can be determined by noting the upward or downward direction of the vertical excursions that followed. Upward excursions represented the presentation of smaller Landolt rings indicating that the animal correctly detected the Landolt "C" within the series of gapless rings in the preceding series. Downward excursions indicated that the animal did not correctly detect the presence of the Landolt "C" and consequently the next series of rings were larger in size. In the lower portion of this same figure the raw data was converted to visual acuity and combined with the data from several other animals. Comparison of average acuity for both the rhesus and human tested under similar viewing conditions is presented and demonstrate the similarity in acuities between these two species over an 8 log unit intensity range.

Prior to exposure, visual acuity was measured under a variety of background conditions. In Figure 4, visual acuity is plotted as a function of the percent contrast between the background and the target. Varying contrast levels were produced by flooding the rear projection screen with light from a second, diffusing projector. The overall luminance of the field was adjusted for equal energies. The data presented is for one animal and baseline measurements were made over a period of several weeks for the animal's two eyes.

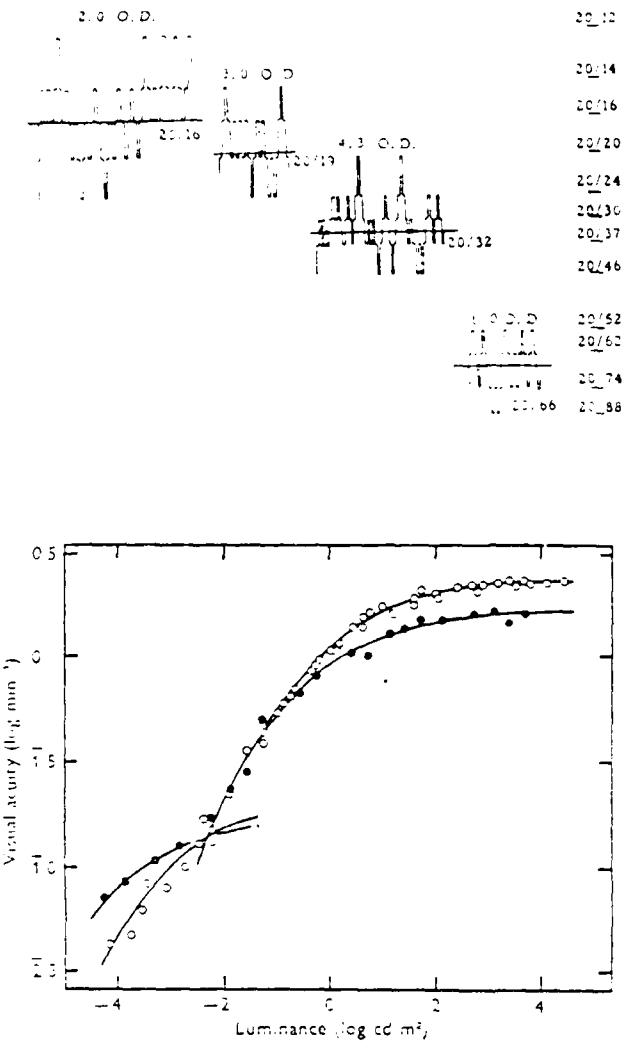

Figure 3. Sample raw data demonstrating the relationship between luminance and acuity. In the upper portion of the figure, the number above each plot represents the neutral density attenuation (in log units) of the raw beam from the maximum photopic conditions possible. In the lower portion of the figure, visual acuity is plotted as a function of the background luminance. The closed circles represent the mean acuity of five rhesus prior to laser exposure while the open circles represent the mean acuity of five human observers tested under similar viewing conditions. The lines through the data were calculated using the Hecht (39) photochemical equation.

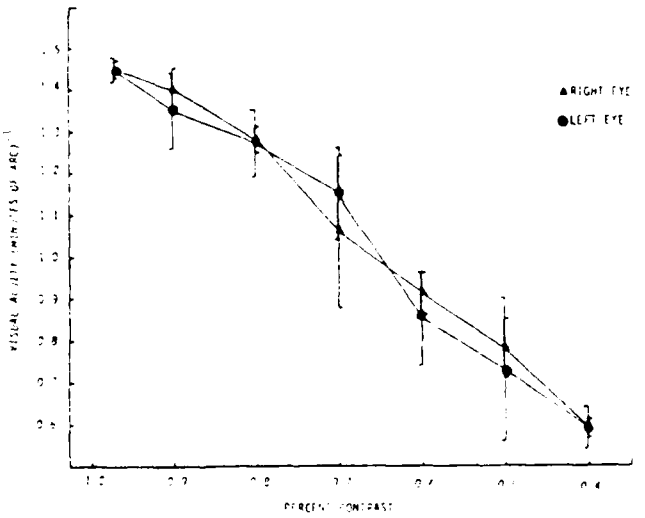

Figure 4. Visual acuity as a function of varying target contrasts for the two eyes of one animal prior to laser exposure. Contrast sensitivity was measured for each eye independently and each data point represents the mean acuity for several different test sessions. All backgrounds were equated for equal luminance. The vertical lines drawn through the data points represent ±1 SD for each eye.

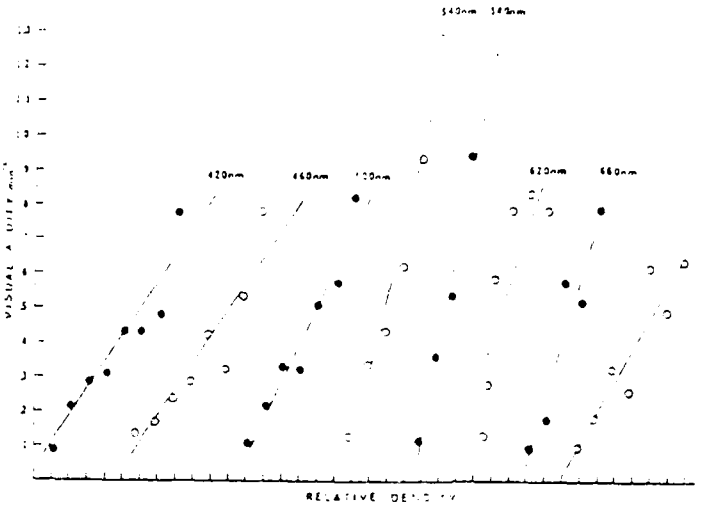

Figure 5. Monochromatic intensity-acuity functions for one rhesus subject prior to laser irradiation. Data is from one animal tested over a period of several weeks. Error bars were derived but not included. Wavelengths and luminances were randomly presented.

Pre-exposure spectral sensitivity was also derived for each animal prior to exposure. Least squares lines were fitted to the linear portion of each intensity/acuity function (Figure 5) and spectral sensitivity curves (Figure 6) were derived using different acuity criteria. In the upper portion of Figure 6, a mean photopic spectral sensitivity curve for several rhesus is shown. Peak sensitivity was at 540 nm although the shape of the curve was rather flat between 500 nm and 560 nm. Sensitivity appeared to drop off more expeditiously at the longer than the shorter wavelengths and this is generally characteristic of the long wavelength insensitivity of the rhesus especially at higher acuity criteria. Comparisons of rhesus, normal human trichromats, and protanomals tested under similar viewing conditions is shown in the lower portion of this figure (Figure 6 B,C,D). Comparisons of the maximum spectral sensitivity for the rhesus, normal human, and protanomalous human showed rather broad peak sensitivities between 520 nm and 560 nm when normalized at 540 nm. No significant shifts in peak sensitivity were noted across the relatively wide range of criterion acuities selected for any group of subjects although changes for all were noted in the breadth of the sensitivity curves. In the long wavelength region of the spectrum, the sensitivity of the human trichromat and the rhesus were nearly identical for the coarsest criterion presented (0.11) and both were nearly one log unit more sensitive than the human protanomal in this spectral region. With a finer criterion acuity (1.11) the rhesus was as much as 2.0 log units less sensitive than the normal trichromat and even less sensitive than the human protanomal in this spectral region. For the shorter wavelengths, however, the rhesus and human protanomalous sensitivities were similar across most acuity criteria and both were slightly more sensitive than that of the normal human trichomat.

A brief exposure of the fovea to a relatively low energy laser flash produces an immediate shift in visual sensitivity followed by a gradual recovery over time. A typical example of this effect using a 100 msec flash of 632.8 nm light is shown in Figure 7. This figure demonstrates the ability of one animal to track acuity immediately following exposure. Time, relative to exposure, is indicated on the abscissa. A pre-exposure mean acuity of 1.25 $(\text{min of arc})^{-1}$ was measured during the first 15 minutes of testing using a 4:1 ratio of gapless rings to Landolt C's (left portion of figure). Immediately preceding the exposure, the S was transferred to a 2:1 ratio of gapless rings to Landolt C's and tested for an additional 2 min. This ratio shift was typically used to more rapidly assess acuity shifts and did not affect either the animal's response criteria or false positive rate. In this session, the animal was exposed to a single 100 msec laser flash following the correct detection of a 1.16 $(\text{min of arc})^{-1}$ Landolt C which corresponded to the zero point on the abscissa of this figure. Immediately after exposure, the animal's acuity decreased to 0.51 $(\text{min of arc})^{-1}$, which corresponds to an acuity deficit of 59% relative to its pre-exposure acuity. This

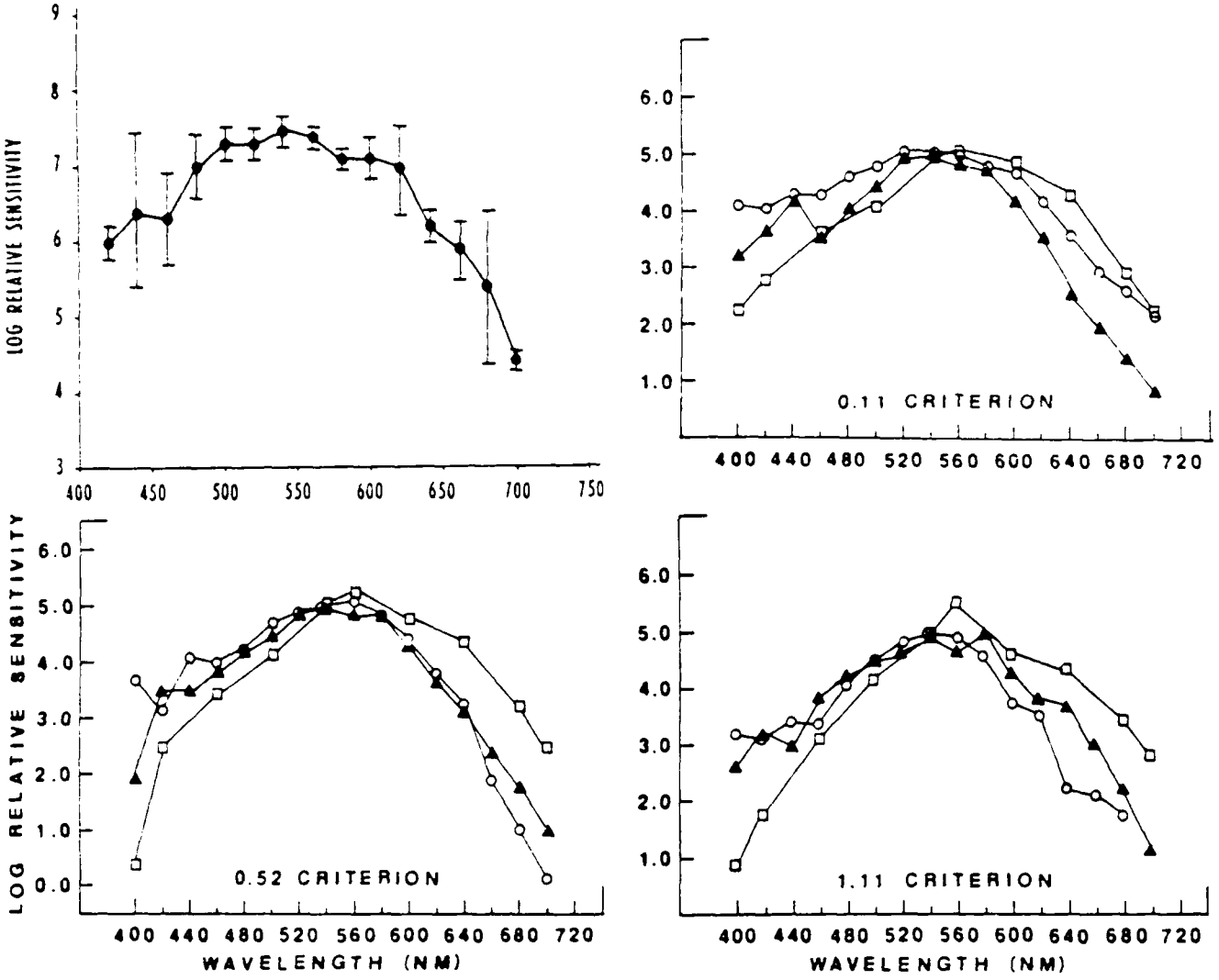

Figure 6. Spectral sensitivity curves for rhesus, human trichromats and protanomalous humans tested under similar viewing conditions. The upper left figure represents the mean spectral sensitivity for several rhesus subjects. The vertical bars drawn through the data points represent the one standard deviation on either side of the mean. In the other figures (3), comparisons using three different criterion acuities are shown for rhesus, human trichromats, and protanomalous humans. For each selected criterion acuity, all spectral sensitivity curves were equated at the 540 nm point which was the usual maximum spectral sensitivity observed. Comparisons made on an absolute basis yielded similar results but are not shown here. Each data point represents the interpolated sensitivity corrected for quantal output as derived from the mean regression equation of the combined individual intensity acuity function for each wavelength for each subject.

visual deficit lasted 9 min before the subject's acuity gradually returned to its mean pre-exposure level. Total recovery from the initial deficit was complete in approximately 13 min. Threshold testing using the 2:1 ratio of gapless rings to Landolt Cs was continued for 3 additional minutes. The ratio of gapless rings to Landolt Cs was then shifted back to 4:1, and postexposure acuity measurements were extended for an additional 15 min. No permanent shift in pre- and postexposure acuity was found at the energy level (7 mW) used in this figure.

Using different laser systems including HeNe, Krypton, Argon, and Nd/YAG, we have explored the relationship between the magnitude and duration of any elicited deficits and the energy of the exposure. For descriptive purposes, the observed recovery process has been divided into two portions, an initial, rapid decline and eventual stabilization of acuity lasting anywhere from several minutes to hours followed by a gradual recovery to pre-exposure acuity levels for those energy densities where full recovery was observed. In those instances where recovery was not observed, typically the animal's postexposure acuity stabilized at the initial depressed acuity level often for several months before any further changes were noticed.

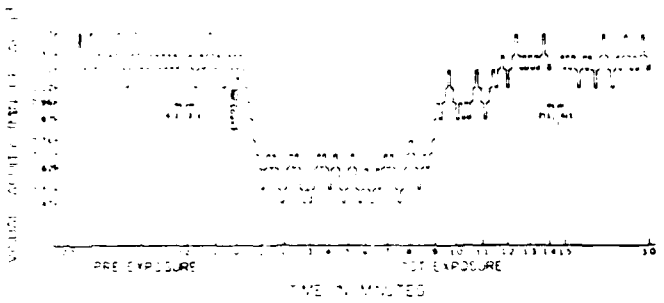

Figure 7. Sample raw data demonstrating the immediate drop in visual acuity following laser irradiation. The occurrence of the 100 msec, 7mW, 632.8 nm exposure is indicated in the figure by an arrow, and corresponds to the zero point on the abscissa. The ordinate indicates the various sizes of the gaps in presented Landolt rings and is plotted in reciprocal visual minutes of arc. This scale is measured in discrete steps, since the vertical excursions of the plot were taken from a non linear potentiometer mounted on the slide tray of a carousel which recorded tray position. The abscissa represents the presentation of the Landolt Cs; corresponding times (in minutes) for representative trials are indicated relative to exposure.

The time course of changes in acuity immediately following four different energy levels of laser irradiation are shown in Figure 8. This figure represents the typical manner in which the elicited deficits in acuity were analyzed. Visual acuity deficit is defined as the percentage decrease in mean postexposure acuity for each running two minutes of testing when compared to the animal's pre-established, mean baseline acuity for the specific type of viewing condition used. In this example (Figure 8) the animal was exposed repeatedly over a period of several weeks to single, 100 msec pulses of 647 nm (Krypton) coherent light ranging in corneal energy from 1.0 to 6.0 mW. No more than one 100 msec exposure was made per session (day) and, for the energy densities shown, recovery was always complete within the 2 hr testing session. Each data point represents the mean of a minimum of four different exposures and, under the conditions shown, variability between sessions was quite low. Acuity, using the tracking technique, was measured using high contrast targets (97%) on a 560 nm monochromatic background. Similar recovery functions were observed using other monochromatic and achromatic backgrounds although the magnitude of the initial deficit as well as the time course for full recovery was related to the type of viewing condition employed to assess visual functioning.

Immediately after exposure, acuity dropped to approximately 70% of its pre-exposure level and, depending upon the energy of the flash, remained at this depressed level for several minutes before gradually returning to its pre-exposure baseline level. During the course of the deficit, the animal appeared vigilant and did not alter his detection criteria as seen in an unchanged false alarm rate. Sham exposures in which the paradigm was identical but the laser flash was not delivered to the eye yielded no change in A permanent deficit produced in one animal is shown in Figure 9. This deficit was produced following several exposures to an 11 mW Krypton flash. Similar to the recovery functions shown previously, immediately after exposure the animal's acuity dropped to approximately 55% of its pre-exposure level but, unlike the previous examples, no recovery was evident during the 40 min postexposure session.

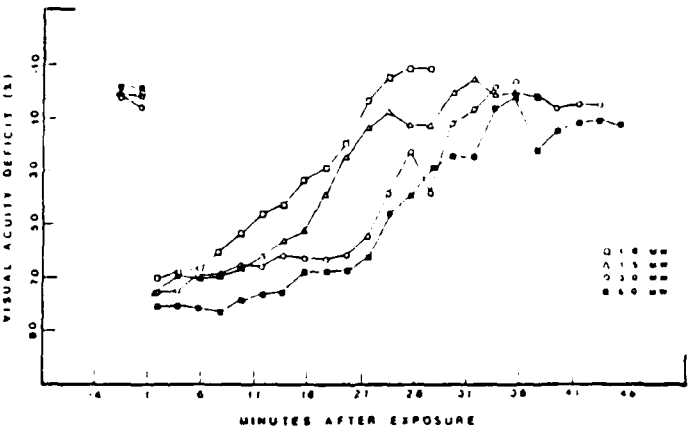

Figure 8. Recovery for several different energy Krypton (647 nm) laser exposures plotted in terms of per cent decrease in visual acuity. The flash duration was 100 msec and all exposure densities were calculated as corneal irradiances. Spot size was 323 microns on the retina. Acuity in the exposed eye was measured under photopic conditions using a high contrast, monochromatic background (560 nm). Percentage deficits for various times immediately following exposure were calculated from the animal's pre- exposure acuity in this eye under these same viewing conditions. Each data point represents the mean of 4-6 different exposures over a period of several weeks. Variability in performance between similar exposures was small.

Twenty four hours following the first exposure session at this energy level, the animal's acuity had partially recovered but still was depressed relative to its pre-exposure level. No further exposures were made and the animal's acuity under a variety of exposure conditions was followed without any additional changes for another 48 hr. After 72 hr, the animal's postexposure acuity returned to normal and remained at this level during several days of acuity testing. The animal was then exposed to a second 11 mW flash and similar to that observed in Figure 8A, recovery again was not complete within the 40 min

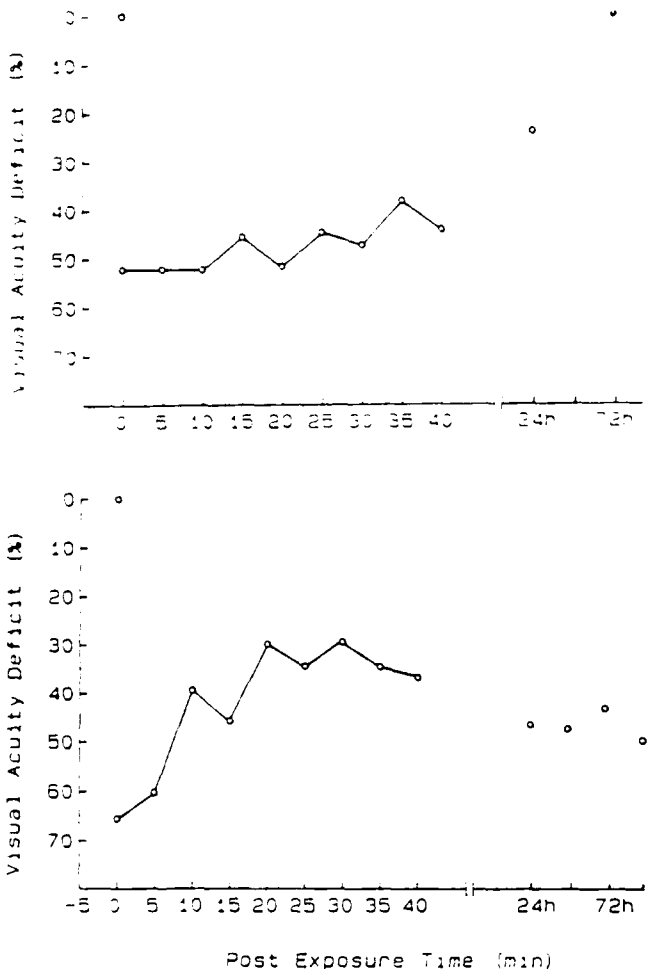

Figure 9. Plots of the decrease in visual acuity immediately following repeated flashes from a Krypton (647 nm) laser at an energy level sufficient to produce a permanent functional deficit. In the upper portion of this figure, the recovery function following the first, 100 msec flash is shown. In the lower portion of this figure, a similar recovery function following the third, 11 mW exposure is shown. This third exposure at this energy level was presented several weeks after the first two exposures. The data points represent the average acuity for each of two running minutes following exposure and are plotted relative to the pre-exposure, baseline level.

postexposure session. Postexposure acuity, however, did eventually recover fully in several days under the various viewing conditions employed to measure visual performance. The animal was then exposed to a third, 11 mW flash and, reminiscent of the other two recovery sessions, acuity did not return to its pre-exposure level during the course of the test session although a minimal amount of acuity recovery was noted after about 15 min. Unlike the first two exposures, no further recovery was noted on subsequent test days and months later the animal's acuity remained depressed in its exposed eye. No shift in acuity was noted for its non-exposed, control eye during this same time period.

Further evidence showing that changes in exposure power density do significantly alter the time course but not the magnitude of deficits is shown in Figure 10. The recovery time course observed here was significantly longer than that usually experienced for photopic bleaching even though the energy level employed was significantly below that necessary to elicit a permanent functional alteration. In this figure the effects of two different power densities of Argon flashes (2.0 mW and 3.0 mW) are shown along with sham exposures (no irradiation). In the sham condition, the size of the projected discriminanda was shifted to the animal's pre-established immediate postexposure acuity level and the animal's acuity was then followed until it returned to its pre-exposure baseline level. In our paradigm, it took approximately 2 min for the equipment to track back to the animal's previous acuity level. When the animal was exposed to laser irradiation, his derived acuity did not recovery immediately but remained depressed before gradually returning to its pre-exposure level. In these instances, the variability across sessions was much larger indicating postexposure performances following laser irradiation were not as predictable as the animal's normal baseline acuity.

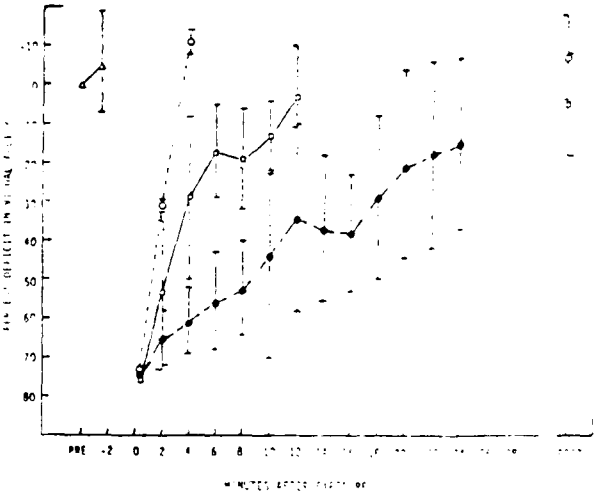

Figure 10. Recovery functions for one animal following 2.0 mW and 3.0 mW Argon (514.5 nm) flashes. Each data point represents the mean of 4-6 exposures. Only one exposure was made per day and a random design for power densities was employed. The open circles represent sham exposures where no laser flash was presented. The squares indicate recovery from 2.0 mW exposures and the dark circles recovery from 3.0 mW exposures. The vertical bars represent a variance of one standard deviation about the animal's mean acuity for that time period following exposure. Acuity was measured under maximum photopic conditions with a high contrast (97%) white light background.

The viewing conditions under which the effects of the laser flash were assessed made significant differences in the magnitude of the initial deficit, the time course of any recovery process, and the likelihood of observing a permanent functional deficit. In this study both the wavelength and contrast of the target were manipulated. In Figure 11, a recovery function derived using darkened targets on a monochromatic background is presented. This animal was repeatedly exposed to 2.0 mW from a Argon laser. Consistent with all other exposures, only one, 100 msec flash was presented per day and postexposure acuity testing began immediately following the exposure and continued until full recovery was evident. The energy level employed was below that necessary to produce a permanent shift in postexposure acuity under this or any other viewing condition. The background contrast level was set at 90%. As can be seen in Figure 11, immediately following exposure, postexposure acuity decreased to approximately 70% of its pre-exposure level and remained depressed at this level for 12 min before gradually returning to its pre-exposure level. In comparison to the achromatic recovery functions shown in Figure 8 for similar energy exposures, the initial changes in acuity remained depressed for a longer period of time when monochromatic backgrounds were used which generally resulted in a longer time for full recovery than when achromatic backgrounds were employed. While the overall differences in recovery were small, they were consistent across subjects and demonstrate the heightened ability of monochromatic backgrounds to detect changes in postexposure spatial resolution.

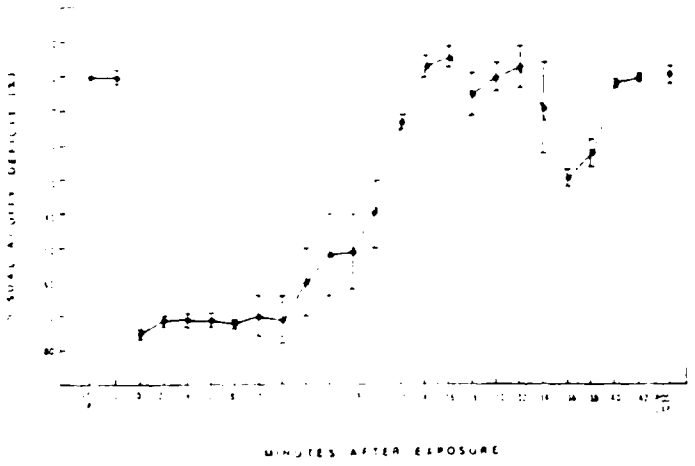

Figure 11. Recovery function for repetitive 2.0 mW Argon (514.5 nm) flashes when measured using a high contrast, chromatic (640 nm) background. Each data point represents the mean of 4-6 individual test sessions. The vertical bars represent ±1 SD on either side of the mean value

The slope and time course of recovery varied with different monochromatic backgrounds. A comparison of monochromatic backgrounds is shown in Figure 12 for one animal exposed repeatedly to 1.0 mW flashes of 647 nm laser light. The maximum initial deficit remained consistent across the different monochromatic and achromatic backgrounds but the duration of the initial deficit and the total time for recovery differed. In this example, recovery was longest when measured using a 480 nm background and shortest when using 560 and 600 nm backgrounds. While differences between the recovery functions derived for each of the different monochromatic backgrounds were small, chromatic background recoveries were significantly longer than recovery for achromatic backgrounds of equal luminance reflecting their enhanced assessment of visual functioning.

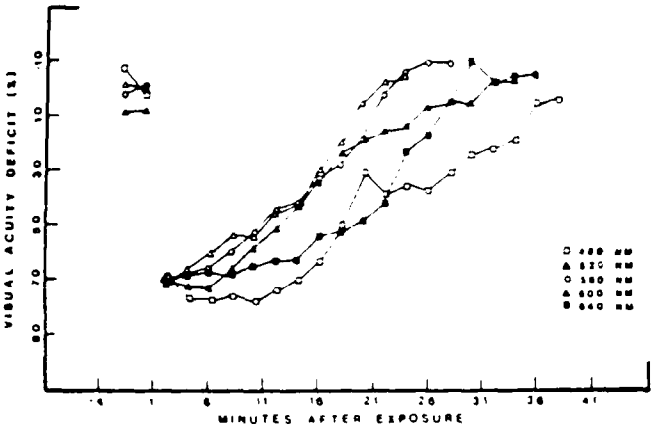

Figure 12. Effects that different chromatic backgrounds have on acuity recovery functions following single 100 msec, 1.0 mW Krypton (647 nm) exposures. Each data point represents the average of 4-6 different exposures. The luminance of the different monochromatic backgrounds were equated and were similar to that used for achromatic backgrounds. This luminance level represented a level of maximum photopic acuity for the animal in this testing paradigm. A random design was used for the presentation of different chromatic backgrounds.

Similar recovery functions for a second animal exposed to more intense 6.0 mW flashes from a Krypton laser are shown in Figure 13. At this energy level, recovery was not always possible within the 2 hr test session. The animal was first tested using a 560 nm background and recovery from an initial deficit of 80% was not complete 45 min after exposure. Twenty-four hours later, the animal's acuity returned to its pre-exposure, baseline level and no additional exposures were made during the next 6 days. A complete battery of post-exposure chromatic and contrast sensitivity measures during this time period revealed no significant deficits in visual sensi-

tivity. On the seventh day, the animal was exposed to a second 6mW flash and recovery, tested with Landolt rings superimposed on 480 nm backgrounds, was complete within 26 min of the exposure. One day later, the same animal was exposed to a third 6.0 mW flash and recovery this time was measured using Landolt rings on a 640 nm background. The immediate recovery function for the third exposure was reminiscent of that observed for the second exposure tested with a different chromatic background. During the initial phase of postexposure testing, the animal's acuity appeared to recover to its pre-exposure level although the animal demonstrated greatly increased variability in performance and a slightly increased false alarm rate over that normally experienced. Twenty four hours later, however, a deficit of 35-45% was noted in this animal's exposed eye when measured using chromatic backgrounds. At this point

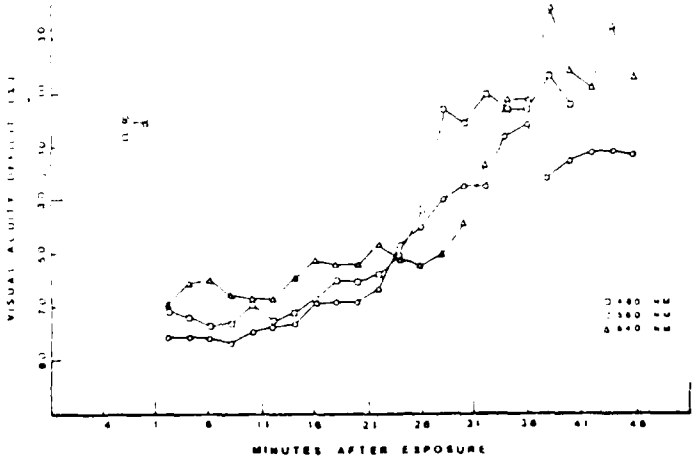

Figure 13. Immediate changes in visual acuity following separate Krypton (647 nm) exposures at the transition point (6.0 mW) for a permanent shift in visual sensitivity. This animal was exposed on three separate occasions to 6.0 mW, 100 msec flashes which represented a retinal beam diameter of 323 microns. Postexposure acuity was measured against three different chromatic backgrounds all equated for equal numbers of quanta. Each data point represents the average for each two minutes of acuity testing. The open circles represent the average postexposure acuity for various times after the first exposure, squares for the second exposure, and triangles for the third exposure. Background wavelength for each of the three recovery functions is shown in the lower right hand portion of the figure.

further exposures were stopped and the animal's postexposure acuity followed for a period of several months. During this time postexposure acuity to all chromatic backgrounds employed remained depressed and no significant recovery was evident. No visual deficit, however, was evident when achromatic backgrounds were employed again demonstrating the enhanced sensitivity of chromatic backgrounds in delineating subtle shifts in postexposure visual performance. No shift in the visual sensitivity was noted in this animal's unexposed eye during this time period.

The inability to demonstrate a permanent visual deficit on the first exposure at a new power density was frequently observed in a number of animals across different exposure and assessment conditions and is suggestive of some sort of cumulative effect. Our paradigm exposed each animal to only one exposure per day of progressively increasing energy once complete postexposure assessments were completed. Typically, an animal might be exposed twenty to fifty times over a period of several months to a specific power density before a new energy level was presented. These repeated exposures were also necessary so that an average recovery function for each of the viewing conditions could be obtained. Within an exposure energy level, the order of presentation of viewing conditions was randomized. No significant differences in the duration or extent of the recovery functions for similar viewing conditions were noted at energy levels below those found to produce a permanent functional impairment. On the contrary, the variability in the recovery data between individual exposures for identical viewing conditions was remarkably low in spite of the time and number of preceding exposures between the functions being averaged. At the transition point between temporary and permanent loss, however, variability between repeated exposures increased significantly indicating the presence of a residual effect which we were unable to directly depict.

Figure 14 demonstrates the residual effects of repeated laser exposures on one animal exposed to 2 mW Argon (514.5 nm) flashes. In this example, the animal had previously been exposed over a period of nearly one year to energy levels which produced no permanent shift in postexposure visual acuity. Following the third exposure to a 2 mw flash, presented over an 8 day period, the animal's postexposure acuity remained depressed for targets on chromatic backgrounds. Following each of the three exposures, the animal's acuity dropped immediately to approximately 75% of its pre-exposure level and remained depressed for the duration of the test session. In each case, the animal experienced a slight recovery (50% decrement) during the first 20 minutes of postexposure testing but further recovery was not evident during the remaining 20 minutes of the session. For the first two exposures, on the next day and several days thereafter, the animal's postexposure acuity recovered to its previous baseline level. Following the third exposure, the animal appeared to recover 24 hours postexposure but in subsequent days, without additional irradiation, the

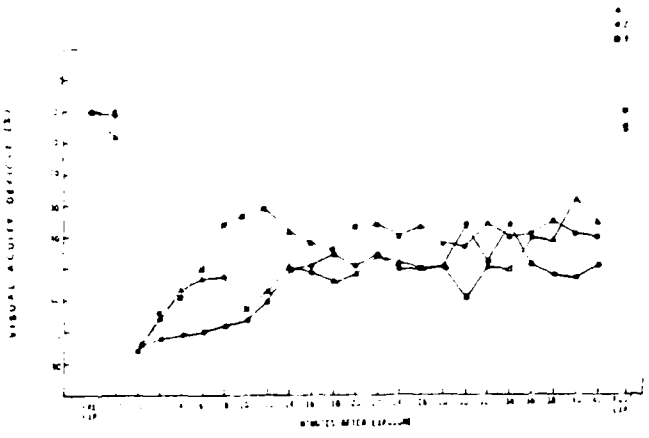

Figure 14. Recovery functions for one animal exposed to Argon (514.5 nm) flashes at the transitional energy level (2.0 mW) for a permanent shift in visual sensitivity. The 100 msec flash of Argon light produced a foveal spot of 323 microns. Acuity was measured using a 540 nm, 90% contrast background. The triangles represent the animal's recovery to the first exposure, the circles to the second exposure, and the squares to the third exposure. The time marked postexposure represents this animal's acuity 24 hr after exposure.

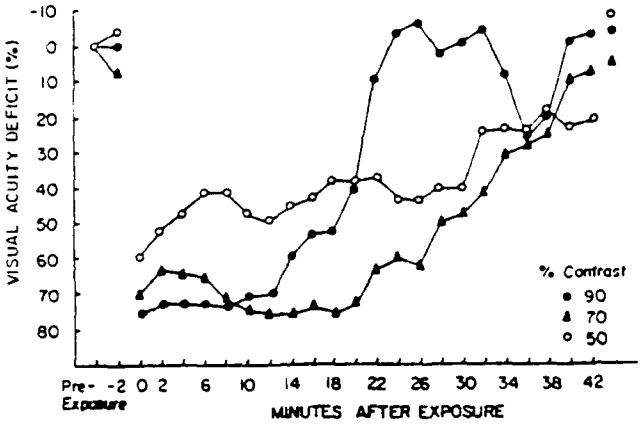

Figure 15. Effects of target contrast recovery following repeated exposures to Argon (514.5 nm) flashes. The diameter of the 2 mW flash on the retina was 50 microns. Three different contrast levels (50, 70 and 90%) were employed. The background of the darkened Landolt ring was 640 nm and each data point represents the average of several exposure sessions. For this exposure condition, recovery was complete within the postexposure session and no significant long term deficit was noted.

animal's acuity in the exposed eye decreased significantly for chromatic but not achromatic targets.

Pre- and postexposure acuities were also measured using chromatic and achromatic targets on backgrounds of different contrast levels. Both the magnitude of the initial deficit and its evident recovery were dependent upon the contrast levels employed. Sample recovery functions for one animal is shown in Figure 15. In this example, the animal was exposed on separate occasions to 2 mW, 100 msec flashes from an Argon laser. Each recovery function is the animal's mean performance level for several exposure sessions. For high contrast targets (90%), postexposure acuity dropped immediately to 75% of its pre-exposure level and remained at this depressed level for approximately 18 min before quickly returning to its pre-exposure level in approximately 26 min. This curve is reminiscent of those shown in previous figures for other high contrast targets. When contrast levels were reduced, the magnitude of the initial deficit decreased (from 75% to 60%) but the overall slope of the recovery functions declined progressively reflecting a longer overall time for full recovery to occur. Furthermore, for the lowest contrast levels employed (50%), the animal's ability to maintain a consistent acuity level was reduced as reflected in a higher session variability for both pre- and postexposure acuity testing.

While the primary exposure variable manipulated was the energy density of the flash, also examined was the position, size, and duration of the exposure on the retina. These changes, like that of exposure energy, had a significant effect on the degree and time course of the recovery function in those cases where full recovery was possible. The effects of changes in the retinal spot size (50 to 323 microns) are shown in Figure 16. In this figure, the exposure energy and duration were held constant as were the viewing conditions under which acuity was derived. These individual recovery functions represent the mean acuities and for clarity, indications of intersession variability are not shown. While this variability was quite small, so also were the averaged absolute differences between different diameter spots on the retina. Within animals, the magnitude of the initial deficit was related to exposure diameter for the three conditions shown here (50, 150, 323 microns). For minimal diameter spots (50 microns), the magnitude of the initial deficit was relatively small (40-50% range) while for larger diameter spots (323 microns) the average deficits ranged from 70% to 80% of pre-exposure acuity. For a given subject, the energy of the exposure had little influence on the magnitude of the initial deficit although, as mentioned elsewhere, the likelihood and time course of recovery were significantly affected. It should be noted that the actual diameter of the laser spot on the retina was somewhat larger than indicated here since the animal's eye was in constant motion during the 100 msec flash. The relatively short duration of this flash did prevent the animal from voluntarily moving his eye away from the bright light source but the rapid, irregular involuntary eye movements naturally occurring during any fixation would have smeared the image across a larger than initially pre-

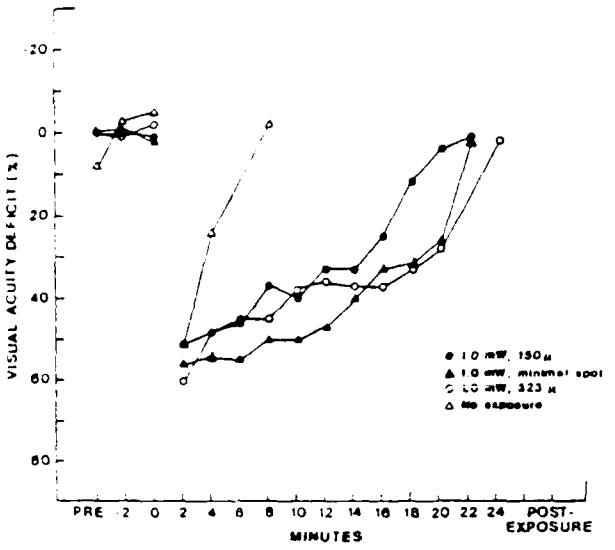

Figure 16. Effects of laser spot diameters on the magnitude and duration of visual deficits following repeated 1.0 mW Argon (514.5 nm) exposures. Each recovery curve was derived in similar manner following a 100 msec exposure positioned on the central fovea. The exposure energy of 1.0 mW was significantly below that which produced a permanent acuity shift. Changes in retinal spot size were produced by changing the expanding telescope and final converging lens in the laser optical system. Acuity was measured using high contrast, achromatic backgrounds.

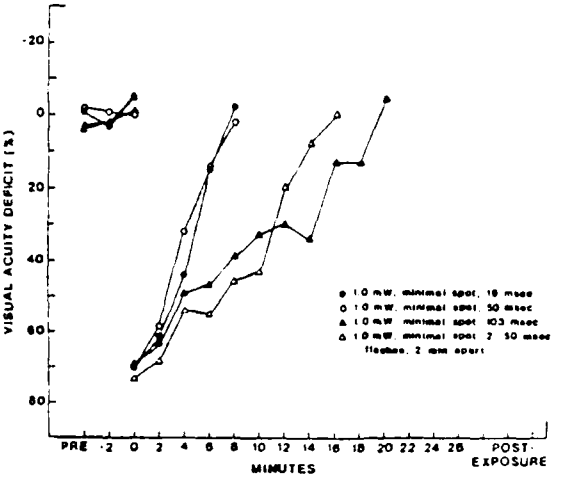

Figure 17. Effects of exposure duration on the post-exposure visual acuity for a minimal diameter, 1.0 mW Argon (514.5 nm) exposure. The individual recovery functions were derived from one animal exposed repeatedly to 1.0 mW flashes of approximately 50 microns in diameter on the retina. Visual acuity was tested using an achromatic, high contrast background. The data points represent means of several different exposures. The durations of retinal exposure employed are shown in the lower right hand portion of the figure. Various durations were produced by a programmable electronic shutter whose pulse duration was measured on a standard storage oscilloscope.

dicted area. Reducing the duration of the exposure below 100 msec might therefore have a significant effect on postexposure acuity especially when relatively small diameter spots are employed since the beam would be spread over a lesser area.

Figure 17 demonstrates the effects that variations in exposure duration can have on the duration of the recovery function when minimal diameter spots (50 microns) are employed. In this figure, the individual recovery functions are shown for different durations of exposure ranging from 19 msec flashes to 103 msec (representing an average 100 msec flash). As the figure shows, recovery to flashes of 19 msec and 50 msec are almost immediate (within 4 to 6 minutes) and represent recovery times not significantly different from the sham condition shown in Figures 10 and 16 (instances where no exposure was presented and instead the animal was allowed to track its artificially depressed acuity back to its previous level). For the longer or repeated exposures, however, the duration of the recovery function for minimal diameter spots was similar to those observed when larger diameter, retinal exposures were administered. It would appear from this data that the consequences of one longer, 103 msec flash was slightly greater than two, 50 msec flashes presented 2 min apart. Such might be the case if eye movements alone were the prevailing catalyst for the effect.

In figure 18 the position of the beam was intentionally positioned away from the gap in the discriminanda and therefore away from the point of central fixation. Under this paradigm, as the position of the beam was placed increasingly off-axis, the duration of the recovery function decreased and when a minimal diameter, 100 msec flash was placed beyond 6 degrees off the point of central fixation, no shift in postexposure acuity was noted. The duration for complete recovery increased systematically as the beam was positioned closer and closer to the point of central fixation.

The previous figures have focused on the transient effects that relatively low energy laser irradiation has on immediate postexposure visual acuity. In these cases, full recovery was typically complete within the 45 min postexposure test session. When higher energy levels were employed, however, full recovery either was delayed for several days or impossible to achieve. In these cases, further exposures were postponed or suspended and complete analyses of postexposure sensitivity were made under a variety of viewing conditions. The laser energy level associated with a permanent functional change was then defined as a threshold value for that particular viewing condition. As previously mentioned, this value varied across laser systems and was different depending upon the type of viewing condition used to assess

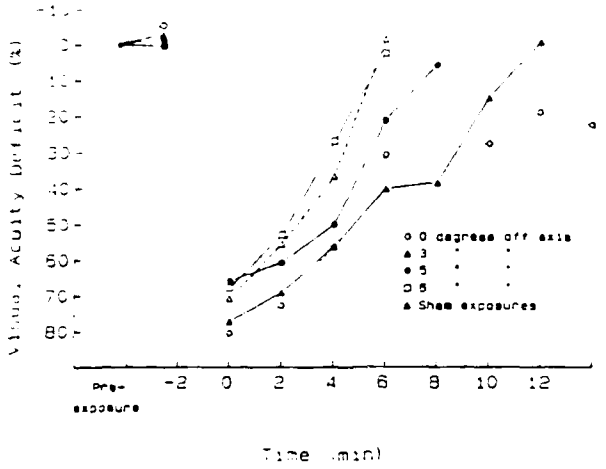

Figure 18. Recovery in visual acuity following 2.0 mW Krypton (647 nm) exposures at various eccentricities. This animal was exposed repeatedly to 100 msec flashes and postexposure acuity was measured using an achromatic background (70% contrast). The recovery curves and the exposure eccentricities employed are indicated.

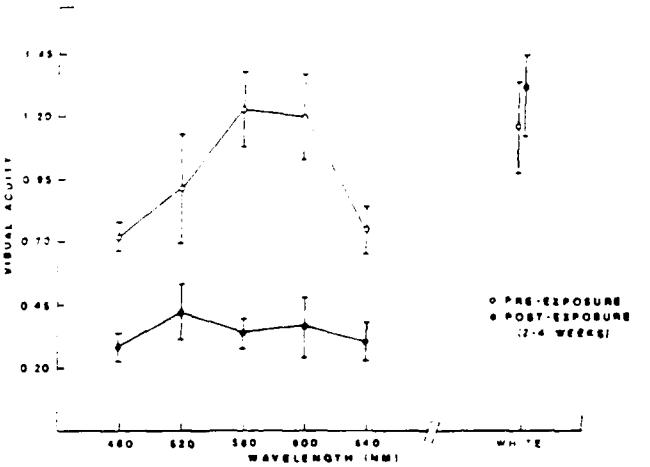

Figure 19. Pre- and postexposure spectral acuity following a 6.0 mW Krypton (647 nm) flash. Spectral acuity was defined as the acuity level achieved for darkened rings superimposed on different chromatic backgrounds each equated for equal numbers of quanta. The overall luminances of the backgrounds were equated to the achromatic backgrounds also used and were at a level which produced the maximum spectral and achromatic acuity. This acuity corresponded to a mean Snellen acuity of 20/17 for this animal. Each data point represents the means of several different test sessions and the vertical bars are ± 1 SD on either side of the mean. The postexposure curve represents the average acuity for each spectral background during the first 4 weeks following laser irradiation.

postexposure acuity. There was also some variability across animals although these differences were relatively small and might be explained in terms of cumulative consequences of preceding exposures which were not necessarily the same across animals.

Generally, the animal's postexposure visual sensitivity following a permanent functional alteration was followed for a period of 6 to 12 months. In those animals that demonstrated a functional impairment that lasted longer than 96 hr, full recovery was rarely achieved across all postexposure assessment criteria and day to day variability in the exposed eye was significantly higher than in the unexposed eye.

An example of changes in postexposure spectral acuity is shown in Figure 19. This animal was exposed to several 6.0 mW Krypton (647 nm) flashes prior to any permanent shift in chromatic acuity. Prior to laser exposure, this animal demonstrated a peak sensitivity at 560 nm (open circles) and sensitivities dropped off markedly on either side of this peak. Immediately after exposure to an energy level that produced a permanent effect, the animal's spectral acuity (filled circles) decreased dramatically in all spectral regions and the entire spectral curve flattened. This particular animal was exposed to 647 nm laser flashes. The greatest difference in pre- and postexposure spectral acuity was in the region of the animal's peak sensitivity (560 nm). The least difference was in the short wavelength region of the visual spectrum. In the upper right hand portion of this figure the animal's pre-exposure (open circles) and postexposure (filled circles) achromatic acuities are shown for this same time period. The animal's mean achromatic acuity actually increased slightly relative to both its pre-exposure level and the acuity of the unexposed eye although the differences were not statistically significant. Similar elevations in achromatic acuity were found in several other animals that demonstrated permanent spectral deficits.

The overall spectral acuity of this and other animals did change over the course of several months of postexposure testing although recovery often was not complete within a year of exposure.

In Figure 20 changes in spectral acuity over several months are shown for another animal exposed to an Argon flash. Similar to the examples shown above, immediately following exposure (filled circles), the entire spectral acuity function was depressed. With time, recovery was observed in all spectral regions tested except the short wavelength region.

Complete spectral sensitivity curves derived from intensity/luminance are shown in Figure 21 for one animal exposed to a threshold dosage from an Argon (514.5 nm) laser. The different curves represent different acuity criterion (0.76, and 1.11). Preexposure peak sensitivity for this animal was 520 nm but shifted somewhat toward 560 nm when

higher acuity criteria were employed. Sensitivity to both short (below 480 nm) and long wavelengths (beyond 560 nm) dropped off rapidly for all criteria employed. Postexposure spectral sensitivity for this animal was derived during the first month following the last laser exposure. Peak spectral sensitivity during this postexposure period shifted markedly to 560 nm for all criteria employed and postexposure acuity in this spectral region, adjusted for luminance, was slightly higher than the animal's pre-exposure level. The maximum shift between pre- and postexposure spectral sensitivity was found in the neighborhood of 500 to 520 nm which corresponded to the wavelength of the exposing source (514.5 nm). Significant decrements in postexposure spectral sensitivity were also found for long wavelengths (beyond 580 nm) and these decreases were greater than those observed for short wavelengths for all criteria shown.

The exposure paradigm used in the previous figures was meant to simulate what consequences a single, brief laser flash might have on visual performance. The energy densities of these exposures were significantly above that ordinarily associated with full retinal bleach but typically below the ED_{50} for distinct morphological damage. In the next series of figures we have examined the consequences of lower energy but longer exposures. This type of paradigm simulates what one might find when attempting to fixate on a target seen through a "cloud" of laser light. We have used the term "cloud"

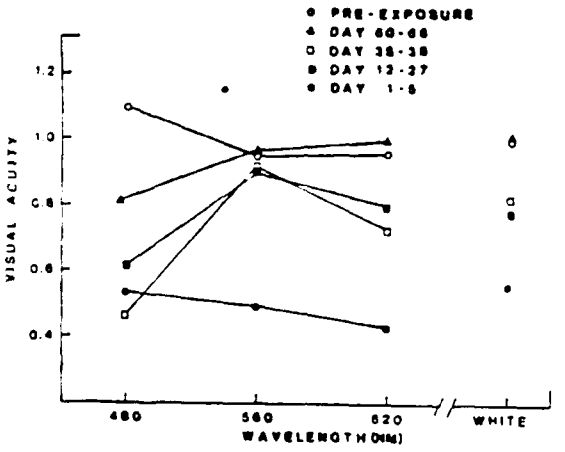

Figure 20. Changes in mean postexposure spectral acuity over several months of testing following exposure to a 100 msec, 3.0 mW Argon flash. The overall luminances of the monochromatic backgrounds were equated to the achromatic backgrounds also used and were at a level which produced the maximum spectral and achromatic acuity. This acuity corresponded to a mean Snellen acuity of 20/18 for this animal. This animal was tested daily during the first two months of postexposure testing and each data point represents the mean acuity during that time period. Other spectral backgrounds were also employed but are not shown here.

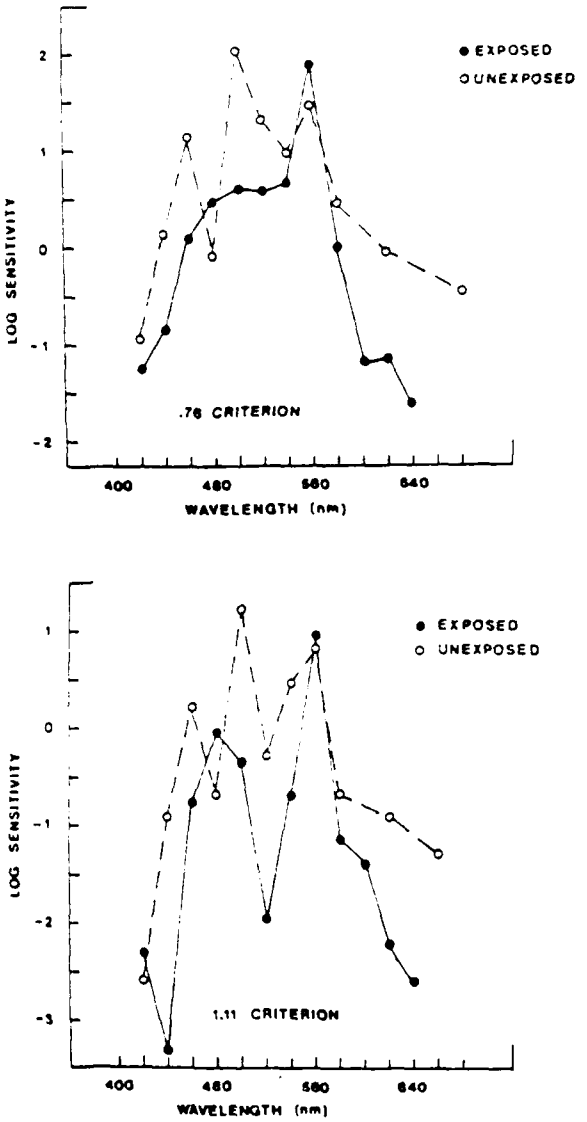

Figure 21. Comparison of pre- and postexposure spectral sensitivity in an animal exposed to a 100 msec, 3.0 mW Argon (514.5 nm) flash. Spectral sensitivity curves were derived from individual intensity/acuity functions determined at each of specific wavelengths shown. Each intensity/acuity function was the average of several days of postexposure testing at each of at least five different luminance levels over a 5.0 log unit range. A repeated measures, rapid design was employed during both the pre- and postexposure test session. The open circles represent pre-exposure sensitivity while the filled circles represent postexposure sensitivity. The criterion chosen are representative of maximum (photopic) and intermediate acuity levels.

even though the light is a point source since the animal's involuntary and voluntary eye movements would spread the laser irradiation over a significant portion of the retina.

A typical example of a visual impairment associated with this type of exposure is shown in Figure

22. This figure is a computer printout of our up-down tracking procedure and shows the animal's baseline acuity prior to, during, and immediately following exposure. Acuity was derived using standard Landolt rings on low contrast, achromatic backgrounds. Pre-exposure acuity for this animal under these viewing conditions was approximately 0.833 (min of arc)$^{-1}$ or 20/24 (in Snellen terminology). At the time marked "0" on the abscissa, the exposure was begun and it was terminated 10 min later. As shown, acuity decreased to approximately 0.15 (min of arc)$^{-1}$ or a Snellen acuity of 20/130 during the first 5 min of exposure. The acuity of this animal remained at this depressed level for the duration of the exposure (10 min) before gradually returning to the animal's original acuity level in approximately 10 min after the laser irradiation was terminated. The rate of recovery following the termination of the laser exposure was reminiscent of that seen for brief, 100 msec flashes. The maximum visual decrement elicited was 82% and may represent the visual resolution of peripheral areas as more and more central areas became bleached with continued laser exposure. In this and other figures to follow, no shift in postexposure acuity was observed longer than 24 hr after laser termination.

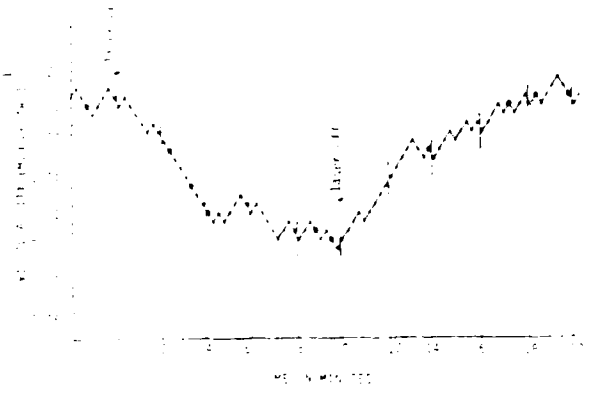

Figure 22. Changes in visual acuity during and immediately following the presentation of relatively low-intensity, long-duration, Argon laser irradiation - glare experiment. This animal was exposed to a 200 micron spot of 0.001 uW for approximately 10 minutes and during this time the animal's acuity was tracked using the up and down procedure. The same optical system as used previously delivered the laser beam in a line coaxial with the gap in the Landolt rings. Hence, the gap which the animal needed to detect in order to make the required discrimination was seen through a "cloud" of laser light. The size of the beam was nearly double the size of the gap for maximum acuity targets when viewed on the screen. The vertical lines through the data represent a running two minute account of time. The closed circles represent the presentation of Landolt "C"s and the vertical excursions the presentation of gapless rings.

Figure 23 demonstrates a similar shift in visual acuity (plotted in terms of percentage deficit) during and immediately following exposure to laser "clouds" of varying (3) energies. When a relatively intense beam (10 uW) was presented, visual performance immediately dropped 90% to an acuity level of 20/140. Not apparent was the continued drop in acuity which was beyond our ability to track. For this reason the laser exposure was prematurely terminated within 4 min of onset. Once off, the animal's acuity slowly returned to its pre-exposure baseline in approximately 10 min without evidence of any permanent deficit. When the "cloud" was made less intense (1 uW), the drop in acuity was slower but, at its maximum, was nearly identical to that seen with a 10 uW exposure. Rate of recovery from these exposure energies was nearly identical in spite of the different presentation durations. For the least intense beam (0.1 uW) the rate of the shift in acuity was similar to that observed with the 1 uW beam but the maximum deficit was significantly less (80%). Again recovery took approximately 10 min once the beam was terminated. The position of the "cloud" covered the enter gap in the discriminanda which made visual resolution of it difficult regardless of the retinal area employed.

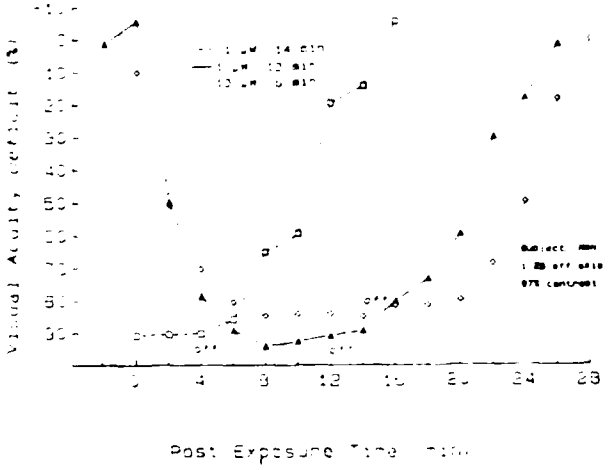

Figure 23. Shifts in baseline acuity during and immediately following low intensity, Argon irradiation at three different power levels - glare effect. This animal was exposed to a 200 micron spot of 10.0, 1.0, or 0.1 uW. The 10.0 uW exposure was presented for 5 min; the 1.0 uW exposure for 13 min and the 0.1 uW exposure for 14 min. During this time the animal's acuity was tracked using the up and down procedure. The data points represent the mean of each running two minutes of acuity testing.

In the next series of figures the position of the laser "cloud" was positioned further off-axis (2^{o}) to facilitate the animal's ability to track his visual

acuity in the presence of the laser irradiation. In Figure 24A and 24B, "clouds" of two different energy levels are shown for discrimination presented against various contrast, achromatic backgrounds. With a less intense laser exposure (.001 mW), acuity for both low and high contrast targets decreased almost immediately following the onset of the exposure to an acuity level of approximately 30 to 50% of the pre-exposure level. In most cases, the animal's acuity remained at this level or improved only slightly until the laser exposure was terminated. Recovery was then rather rapid and the animals demonstrated no residual effect following this type of exposure. For more intense exposure energies (Figure 24B), acuity for high and low contrast targets decreased 70 to 85% and remained depressed during the entire duration of the exposure. As with less intense exposures, recovery was rapid and complete once the exposure was terminated.

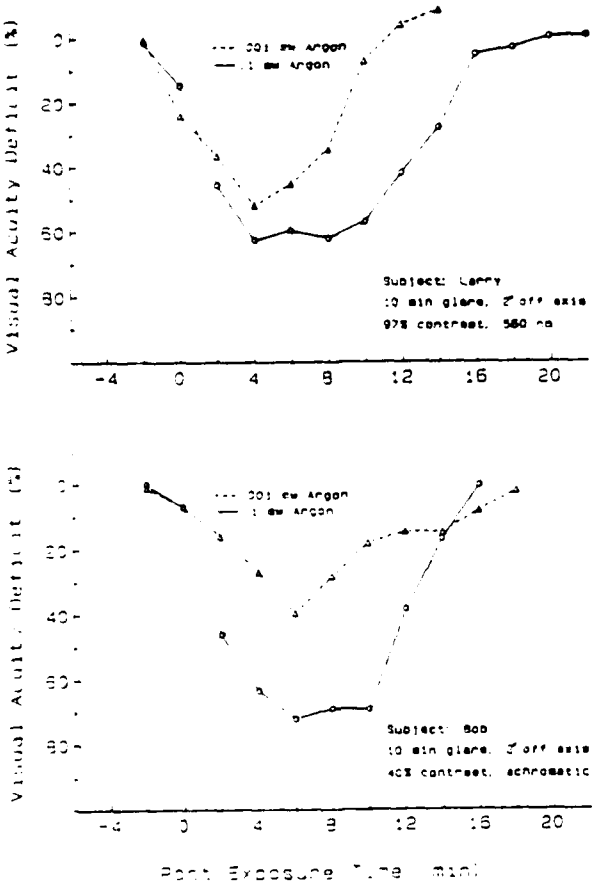

Figure 24. Shifts in visual acuity measured with different contrast backgrounds during and immediately following low-intensity, 10 min Argon exposures - glare effects. The exposure energies were 0.001 mW (A) and 0.10 mW (B) and were centered 2° off axis although the beam still partially covered the gaps in the Landolt rings. All backgrounds were equated for equal overall luminances.

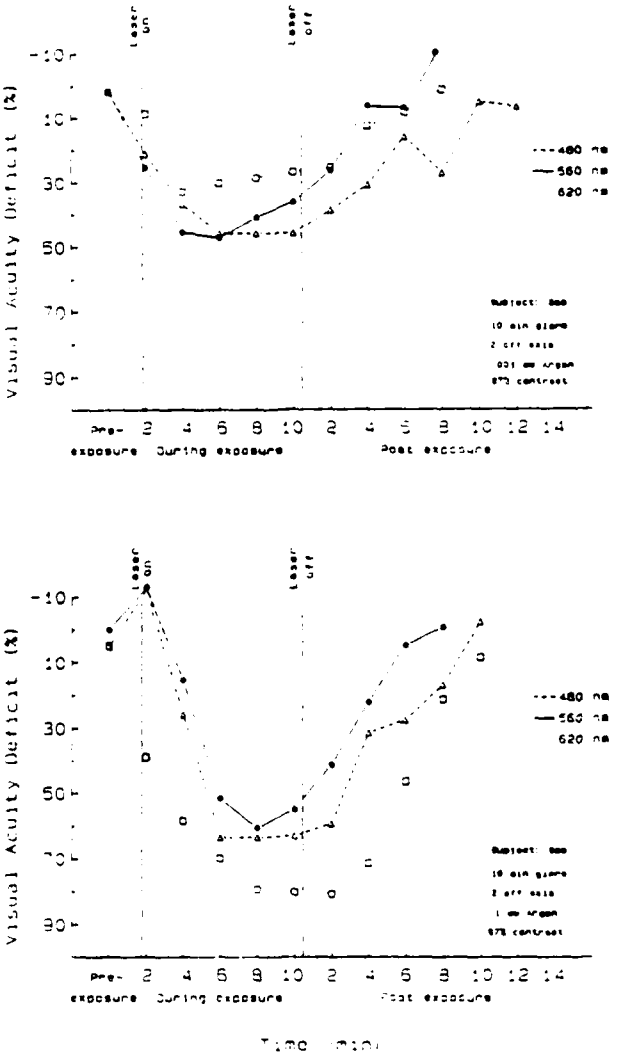

Figure 25. Shifts in visual acuity measured with different chromatic backgrounds during and immediately following low intensity, 10 min Argon exposures - glare effects. The exposure lasted 10 min and was centered 2° off axis although still covering the gap in the Landolt rings. The onset and termination points of the 10 min laser irradiation are shown by dotted lines. The upper graphs represent the mean running acuity following a 0.001 mW 514.5 nm exposure while the lower graphs represent the mean acuities following a 0.1 mW exposure. The different monochromatic backgrounds were equated for equal numbers of quanta and were presented under maximum photopic conditions. Acuity was tracked using the up and down procedure during the entire course of laser irradiation.

A similar series of figures are shown in Figure 25A and 25B for three different, high contrast monochromatic backgrounds (480, 560, 620 nm). Unlike the previous figures, the greatest overall deficits were seen not by variations in exposure energy (0.001 mW vs. 0.1 mW) but by the specific

monochromatic background used to assess visual acuity. Visual acuity decreased the greatest when the laser 514.5 nm "cloud" was superimposed over a 620 nm background. Independent of exposure energy, the subject's acuity decreased to approximately 90% of its pre-exposure level and remained depressed for the duration of the 10 min exposure. For 560 nm backgrounds, on the other hand, acuity decreased to approximately 60% of its previous level and the animal's acuity gradually improved while the "cloud" was still being presented. Recovery, however, occurred within 10 min of the termination of the exposure in all cases and no residual effect was noted.

DISCUSSION

Using different laser systems, we have explored the initial effects brief exposures focused on the fovea have on visual acuity. Our results show that the magnitude of the deficit was related to the size and duration of retinal exposures while the time necessary for recovery, when possible, was a function of the exposure energy.

The methodology developed during a previous research project (40) and modified during the current effort appeared suitable for producing foveal exposures in awake, task oriented animals. This method allowed for the measurement of rhesus visual acuity immediately following laser exposure thereby allowing for the exploration of the effects of exposure energies at and below the ED_{50}. Over 90% of the exposures produced an immediate drop in visual sensitivity reminiscent of the maximum permanent dficits observed in other studies using more intense irradiation and anesthesia to place the exposure directly onto the fovea (11, 32). In those few cases were no immediate shift in acuity was observed, one might speculate that either involuntary or preinitiated voluntary eye movements resulted in irradiation of extrafoveal areas. The irradiation of these areas should produce little if any shift in maximal acuity since only foveal areas are normally involved in the detection of minute spatial detail. It is also possible that lid closures, especially when subthreshold energy levels were employed, might have resulted in reduced foveal involvement and hence produced only minimal shifts in visual acuity immediately following exposure.

Once exposed, our animals maintained vigil and continued to respond despite their often reduced visual sensitivity. Further, our data suggest that our animals did not change their criterion for detection (beta value) of the critical feature in the Landolt ring, as indicated by their unchanged false alarm rate for targets below their new threshold level. What did change was the animal's sensitivity (d') to resolve this spatial task. The lack of a total functional impairment implies that the animals quickly learned to employ alternative, unexposed retinal areas to make the required discrimination. Given the size of our exposing beam, these areas would normally be outside the foveal region, in areas where spatial resolution is reduced. The magnitude of the initial deficit and its dependence on beam diameter supports this para foveal hypothesis.

An alternative hypothesis, however, might be that laser exposure resulted in an incomplete saturation of the photo receptors and the resultant acuity levels obtained represented the activity of nondepleted foveal photoreceptors. Recovery would then represent the time required for affected foveal photoreceptors to again become fully functional. If this hypothesis was correct, however, one would expect that both the magnitude and the duration of any elicited deficit in visual acuity would be dependent upon exposure energy. Our results clearly indicate that only recovery time was related to exposure energy suggesting that the former, parafoveal hypothesis, more accurately accounts for our observed visual deficits.

The relatively large deficits (50% to 90%) produced by even our minimal diameter beams (50 micron spot on the retina) demonstrate the influences that involuntary eye movements have on the area of involvement even during central fixation. The relatively short duration of this flash (100 msec) did prevent the animal from voluntarily moving his eye away from the bright light source but the rapid, irregular involuntary eye movements naturally occurring during any fixation would have smeared the image across a larger than initially predicted area. This might explain why even relatively small diameter retinal exposures (50 microns) produced a some what larger and longer decrement in postexposure visual acuity than might otherwise be expected. Without these movements or with shorter duration exposures one would expect not to observe any shift in postexposure acuity when minimal diamater (50 microns) exposures are used. Reducing the duration of the exposure below 100 msec might therefore produce less or no deficit in postexposure acuity especially when relatively small diameter spots are employed. Increasing the exposure duration above 100 msec, on the other hand, might be expected to have no greater effect over those observed since, for these longer durations, the animal's voluntary movements might reduce its foveal consequences.

With very short duration exposures (< 50 msec) little or no observed temporary deficits in visual

acuity were observed for those energy levels that were below the ED_{50} level. In subsequent research we have shown that very intense exposures (energy densities significantly above the ED_{50}) also have no significant effect on visual acuity although the animal's performance, perhaps due to restricted foveal lesions, becomes more erratic. Multiple exposures of this nature should eventually produce a consistent long term drop in postexposure acuity as the lesion site increasingly spreads across the fovea.

The notion that the area of foveal involvement, whether as the result of changes in beam diameter or exposure duration, has a significant effect on the magnitude and duration of any observed acuity deficit, was also supported by our off-axis experiments. Intentionally positioning the beam away from the animal's point of central fixation (off-axis) decreased both the magnitude and duration of any elicited acuity deficit. Depending upon the degree of eccentricity we have been able to measure baseline sensitivities of more peripheral regions of the retina.

Our paradigm was most applicable for the behavioral assessments of exposures restricted to the fovea, not parafoveal or peripheral retinal regions. A more complex visual target, requiring multiple discriminations but still requiring central fixation would be necessary for off-axis exposures and peripheral acuity assessments. We have begun exploring the possibilities of both peripheral exposures and assessments of peripheral resolutions using multiple visual discriminations presented simultaneously.

For those foveal exposures where only transient changes in visual acuity were seen, the duration for full photopic recovery was often significantly longer than that typically observed in human psychophysical studies employing full bleach. The average duration for our transient effect was 20 minutes and is much longer than the 3 to 5 min adaptation time characteristic of these types of studies. This relatively long recovery time suggests that aberrant photochemical changes and/or neural processing were operating which involved a longer than usual time to reverse. As indicated below, the increased susceptibility to repeated exposures separated in time by periods in excess of 24 hr also suggests that atypical changes were elicited by the exposure levels used. These photochemical and/or neural changes in all likelihood extended beyond the observed time course for recovery and are reminiscent of the long term consequences that chronic exposure to loud noises have on the auditory system.

In comparison to achromatic acuity, when chromatic acuity (darkened Landolt rings on spectrally different, monochromatic backgrounds) was employed, the initial deficit in acuity remained depressed for a longer period of time. These differences suggest that chromatic acuity testing was more sensitive a measure of overall foveal functioning than achromatic acuity. This is consistent with the notion that the fovea consists largely of cones, each with selective spectral absorptions characteristic of the type of visual pigments within their outer segments. Furthermore, the convergence of neural signals from these receptors optimize wavelength discriminations and chromatic spatial resolution and imply that post exposure changes in chromatic acuity should be more severely altered by laser irradiation than should achromatic acuity. For both Krypton (647 nm) and Argon (514.5 nm) exposures, generally recovery was longest for the very short (480 nm and below) and very long (640 nm and above) background wavelengths than for chromatic backgrounds in between. This effect was consistent across different exposure energies. The relatively larger effect of both short and long wavelength backgrounds could be explained in terms of fewer numbers of foveal receptors in these spectral regions.

At the transition point for a long term functional impairment, permanent deficits were noted for chromatic acuity when no such changes were observed for achromatic acuity. Postexposure chromatic acuity deficits of 30% to 50% remained unchanged for 6 to 12 months after exposure in animals that demonstrated no significant shift in achromatic acuity. The inability to observe any longterm deficit with achromatic targets also suggests that chromatic acuity is a more sensitive measure of overall foveal funtioning. While there were shifts in chromatic acuity over time, generally little recovery was seen in those cases were a permanent loss was produced.

In those instances where recovery was not observed, typically the animal's postexposure acuity stabilized at the initial depressed acuity level often for several months before any further changes were noticed. Associated with these losses in visual acuity, was an increased variability of performance in the exposed eye within and between sessions. Such changes might be explained by the animal's attempt to develop new strategies to compensate for the loss of normal foveal functioning. As the animals learn to make the required discrimination in the parafoveal retina his performance should improve slightly with time as was the case in many of our exposed animals. Nevertheless, animals exposed to damaging levels of laser light appeared much more reluctant to begin acuity testing than before. They were more difficult to capture and dress (fit with helmet) and were much more aggressive in behavior. Performance was somewhat less consistent and the animals displayed more anxiety

over the task as demonstrated by increased vocalizations and movements during testing with the exposed eye. Similar changes in visual performance were not seen in the control eye. The loss of the fovea in the exposed eye would certainly make the animal's task more difficult and could increase the animal's anxiety level to the overall testing environment.

The actual energy density required to produce a permanent functional impairment varied across laser systems. Argon exposures (100 msec flashes) typically produced a permanent deficit at lower energy values (2.0 mW) than either Krypton (6.0 mW or HeNe (11mw). All of the energy densities used were below the ED_{50} for distinct morphological damage as reported elsewhere for our exposure conditions. These energy densities, however, were significantly above those ordinarily associated with full bleach in light adaptation experiments. As expected, fundoscopic examination of our animals' foveae revealed no distinct morphological alterations in animals where significant functional impairments were evident. These fundoscopic examination were made both in our laboratory and at the Department of Biorheology, Letterman Army Institute of Research in San Francisco, but were often made several months after the animal's last exposure. The lack of a gross morphological correlate is not surprising and supports our notion that behavioral assessment of visual functioning might be a more sensitive measure of minute changes in retinal functioning than are distinct fundoscopic changes. This is especially true when the behavioral task involves the fine spatial resolution of chromatic targets which are typically associated with foveal cone vision.

The actual threshold level derived, however, was influenced by the type of visual task employed. As previous discussed, chromatic targets were a more sensitive measure of fine foveal dysfunction than were achromatic targets of equal luminance and contrast. Lower contrast targets also generally depicted a larger deficit for those exposures which produced permanent foveal changes but the contrast alone did not alter the derived threshold point for a permanent effect. There was also some variability across animals although these differences were relatively small and might be explained in terms of cumulative consequences of preceding exposures which were not necessary the same across animals. The cumulative effects of repeated exposures separated in time by more than 24 hr were also supported by the fact that a permanent functional deficit was typically elicited not after the first exposure at a specific power level but after repeated exposures, some of which were separated from each other by as much as two weeks time. The actual threshold values derived in this experiment were significantly below those reported elsewhere in which a morphological criterion was used for damage and, together with the possibility of cumulative consequences, suggest that the laser may be more potentially damaging to vision than originally reported. Furthermore, independent of its permanency, the laser can effectively distort foveal sensitivity for periods of time sufficiently long so as to create a major disruption of one's visual/motor behavior. These relatively transient changes might have life threatening consequences depending upon the nature of the mission at hand and must be considered when developing any type of protective device for laser safety.

The appropriateness of the rhesus monkey as a human prototype is well substantiated in this study. The visual sensitivity of this species is essentially the same as that of the human observer. These comparisons are remarkably consistent especially when one considers the numbers of subjects employed and the necessary differences in psychophysical methods used. The achromatic acuity of the rhesus was the same as that of the human except at the extremes of the luminance range. The mean of the standard deviations at each luminance level for five human observers was almost identical to that of the five rhesus. Both animals demonstrated a rod-cone break at the same luminance level and had a similar 8 log unit operating range. While the rhesus visual acuity was slightly superior to that of the human at minimal scotopic ranges and the human slightly superior at maximum photopic ranges, the overall shape of the functions for the two species was the same. The slight differences at both ends of the continuum might be explained in terms of differential pupil diameters at these intensity extremes. The slightly larger pupil of the rhesus would be an advantage under minimal light conditions but would increase stray light effects under conditions where there is an overabundance of light. At low luminance levels, the rhesus perform as if they were receiving 4-5 times more light than the human observers. The greater efficiency of the rhesus eye to light might effect threshold for laser irradiation but in our experiments any such effect was eliminated by presenting all exposures under Maxwellian view although uncontrolled were differential pigment absorptions that might exist within these species.

The rhesus, like the human, performed optimally under high contrast conditions with performance decreasing monotonically as contrast levels were reduced. The maximum acuity achieved by the rhesus under optimal contrast and luminance levels was 1.45 $(\text{min of arc})^{-1}$ demonstrating that our animals in this situation were highly motivated to perform. This corresponds to a Snellen acuity of

20/14, one that can be seen in humans only under optimal test conditions. The overall shape and peak of the spectral sensitivity curves for human and rhesus were similar although under maximum acuity criteria, the rhesus did demonstrate a reduced long wavelength sensitivity. This insensitivity of the rhesus to long wavelength light is similar to that observed in protanomalous human observers and might explain the greater drop in long wavelength sensitivity following exposure to either long or intermediate wavelengths (Argon or Krypton). Perhaps the rhesus fovea has fewer long wavelength receptors which when irradiated with intense laser light leaves fewer pigments/receptors available in this spectral region than elsewhere. The observed increased baseline sensitivity for the rhesus in the short wavelength region of the visible spectrum, while not statistically significant, might be partially explained in several different ways. The observed species differences in the spectral opacity of the lens and macular pigmentation might increase the effectiveness of the transmission of short wavelength light to the retina. Likewise, a reduction in the amount of neural inhibition on blue receptors from a reduced population of red receptors might neurally increase the short wave length sensitivity of this species (41). Since our laser exposures were limited to intermediate and long wavelength irradiances, any increased effectiveness of the short wavelength light would not be a confounding factor in our comparisons of human and rhesus susceptibility to laser irradiation. While some correction factor needs to be applied when comparing the relative efficiencies of these two species ability to absorb incident light, the perceptual consequences would appear to be remarkably similar.

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